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(71) Applicant *(for all designated States except US)*: **KING'S COLLEGE LONDON** [GB/GB]; Strand, London WC2R 2LS (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JONES, Keith** [GB/GB]; Division of Life Sciences, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 8WA (GB). **WHITFIELD, Philip, John** [GB/GB]; Division of Life Sciences, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 8WA (GB). **ROSSITER, Sharon** [GB/GB]; Division of Life Sciences, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 8WA (GB). **MATTHEWSON, Michael, Derek** [GB/GB]; Schering-Plough Animal Health, Breakspear Road South, Harefield, Uxbridge, Middlesex UB9 6LS (GB).

(74) Agents: **RITTER, Stephen, David** et al.; Mathys & Squire, 100 Gray's Inn Road, London WC1X 8AL (GB).

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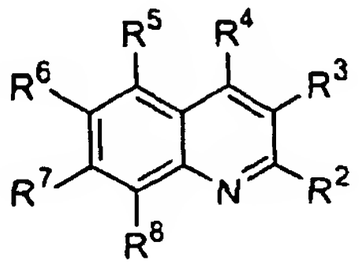
(54) Title: ANTIPARASITIC COMPOUNDS



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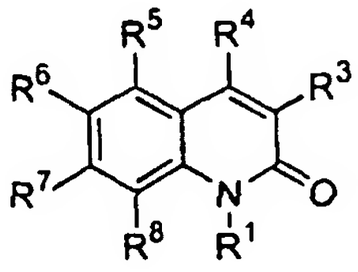

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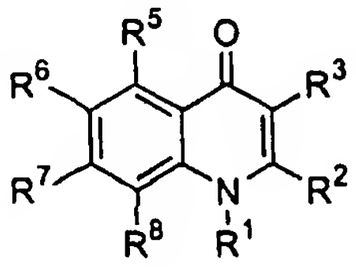


(IB)

(57) Abstract: Disclosed are antiparasitic compounds of Formulae (I, IA and IB). These compounds are useful in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of infections caused by helminths or arthropod ectoparasites.

Antiparasitic Compounds

This invention relates to the technical field of compounds that have antiparasitic activity. In particular, this invention pertains to compounds that have potential use in therapy for the treatment of disease caused by parasitic helminths. This invention also relates to compounds having activity against ectoparasites.

There are three main classes of parasitic worms or helminths – nematodes (round worms), trematodes (digeanians or flukes) and cestodes (tapeworms).

Parasitic helminths can infect vertebrates, invertebrates and plants, causing many diseases of medical, veterinary and agricultural importance. In plants, parasitic nematodes can cause severe mechanical damage to the roots, stems, leaves and flowers of many plants, as well as causing losses in plant crops by opening a path for the entry of bacteria, fungi and other nematodes. Diseases caused by parasitic helminths in humans and other mammals can cause a wide range of pathological effects and symptoms, including abdominal pain, abcesses, anaemia, appendicitis, bronchial asthma, chyluria, conjunctivis, dermatitis, diarrhoea, oedema, elephantiasis, eosinophilia, eosinophilic meningitis, leukocytosis, lymphangitis, myocarditis and neurological effects. Parasitic infections can lead to malnutrition, weight loss, weakness and severe damage to the tissues and organs of the infected host.

Infections by parasitic worms can be extremely debilitating, and in severe cases, may be fatal if left untreated. It is estimated that over one billion people are infected by nematodes worldwide. Most of the infections are in the developing countries of the tropics and sub-tropics. Also of importance are the parasitic helminths that infect livestock. For example, cattle and sheep harbour a number of nematodes, with *Trichostrongylus, Dictyocaulus, Ostertagia, Cooperia* and *Haemonchus* being the most important. Medically important nematodes include *Nematodirus, Ascaris, Bunostomum, Oesophagostomum, Chabertia, Trichuris,*

Strongylus, Trichonema, Dictyocaulus, Capillaria, Heterakis, Toxocara, Ascaridia, Oxyuris, Ancylostoma, Uncinaria, Toxascaris, Parascaris and *Wuchereria*.

The pathological effects and symptoms of the veterinary diseases depend on the identity of the parasitic helminth and the site of the helminth infection. For example, certain of these such as *Nematodirus, Cooperia* and *Oesphagostomum* attack the intestinal tract, whereas *Haemonchus* and *Ostertagia* primarily attack the stomach. *Dictyocaulus* is more prevalent in the lungs. Other parasitic helminths may be located in other tissues and organs of the body, such as the heart, blood vessels, subcutaneous and lymphatic tissue.

In humans, the parasitic disease schistosomiasis (bilharzia, bilharziosis), is a widespread disease in many parts of the world, particularly Africa and South America. It is caused by trematode parasites of the schistosome family, of which *Schistosoma mansoni*, is the most widespread.

The adults of *S. mansoni* live in the mesenteric blood vessels associated with the gut of the human host and lay large numbers of eggs. The eggs have a sharp spine that can break through blood vessels into body tissues, or they can be carried along the hepatic portal vein to the liver, where they cause an immune reaction leading to the formation of granulomata. In severe cases, liver and spleen enlargement ensues, which can be fatal if treatment is not received in time. Other schistosomes cause different forms of illness in humans – for example. *S. haematobium* infects the blood vessels of the bladder, and can cause damage to the urinary system, whereas *S. japonicum* also infects the mesenteric veins around the small intestine.

The life cycle of *S. mansoni* is complex. The eggs of *S. mansoni* are excreted from the body with human faeces, and if they make their way into water, the first larval stages (miracidia), can hatch from the eggs to infect an intermediate host, a water snail. Eventually, subsequent larval stages (cercariae) develop and are released into the water, where they can infect humans by burrowing through the

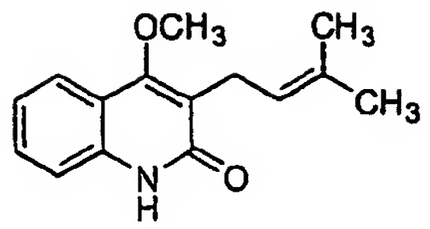
skin, and subsequently are carried through the circulation into the liver. The adults then migrate to the mesenteric blood vessels where they stay for life.

Infection can occur in any standing or slow-flowing water, where the water snails live. It is estimated that over 500 million people in over seventy countries are at risk from the various forms of schistosomiasis, with around 200 million actual infections worldwide, making schistosomiasis a disease of global significance.

It will therefore be appreciated that early treatment is necessary to manage schistosomiasis, and other diseases caused by parasitic helminths. The drug praziquantel is the current drug of choice used to eradicate the adult worms of *S. mansoni*. However, recent studies have shown low cure rates in particular parts of the world, suggesting that the *S. mansoni* parasite is becoming resistant to this drug. Measures to control the population of the schistosome-carrying water snails have had some effect. However, the use of molluscicides on a large scale is difficult logistically and not desirable for ecological reasons. Research to find a vaccine against particular schistosomes, has proved to be difficult because, for example, adult *S. mansoni* are able, by a variety of mechanisms, to evade immune responses. Thus, at present, chemotherapeutic control of parasitic helminths is a favoured approach.

Although the mechanism of action of most anthelmintics are not fully understood in detail, anthelmintics can be broadly classified by their modes of action. Piperazine salts, avermectins, levamisole, and organophosphates interfere with the neuromuscular coordination of the parasites, whereas benzimidazoles such as thiabendazole and albendazole interfere with the assembly of parasitic microtubules.

Certain substituted quinoline derivatives are disclosed to possess anthelmintic activity against specific helminths. Atanine (3-dimethylallyl-4-methoxy-2-quinolinone), an alkaloid isolated from the dried, unripe fruits of *Evodia rutaecarpa* (*Rutaceae*), and having the following chemical structure:



has been shown to be active against cercarial and miracidial larvae of *S. mansoni*, and adults and larvae of the non-parasitic soil nematode, *Caenorhabditis elegans* (*Planta Medica, (1995), 61, 276-278).*

Heterocyclic compounds, including quinoline-based analogues having anthelmintic and fungicidal activity are disclosed in US 3,624,088. The compounds disclosed therein all possess a trichloroethylidine amine functionality i.e. $-N=CHCCl_3$, attached to the heterocyclic ring.

US 3,879,549 discloses a process for the treatment of bilharziosis and filariasis using antimony. According to the disclosed process, the antimony is administered as a salt of a substituted 8-hydroxyquinoline.

US 5,227,387 discloses a method of inhibiting a nematode population in plants comprising applying to the locus of a nematode, a compound of the formula Het-X-CH_2CH_2-Ar, wherein "Het" can include 4-quinolinyl or 8-fluoro-4-quinolinyl, and X can be O, NH or CH_2. The compounds are said to possess nematocidal activity against certain agricultural nematodes compared with the known agricultural nematocides, aldicarb, carbofuran and fenamiphos.

US 5,541,195 discloses a class of 2-substituted quinoline derivatives for the treatment of leishmaniasis, a group of parasitic conditions caused by the *Leishmania* protozoal parasite of the family *Trypanosomatidae*. This document does not disclose compounds having anthelmintic activity.

The development of drug resistance is a major problem with chemical control measures. For example, benzimidazole and levamisole resistance has appeared in Trichostrongyle infections of sheep. Because anthelmintic resistance remains a

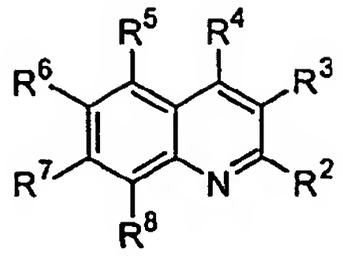
threat to the main form of control of parasitic helminths, there exists an urgent need for the development of new, alternative anthelmintic drugs.

Advantageously, an anthelmintic should have a broad spectrum of activity and have a wide safety margin. Preferably, an anthelmintic agent should be therapeutically effective against all pathogenic stages of a parasitic helminth, including the larvae. Ideally, an anthelmintic should be rapidly metabolised and excreted and be easy to administer.

It is an object of the present invention to provide further anthelmintic compounds, especially compounds that have a broad spectrum of activity, and compounds that are effective against organisms that are resistant to available drugs. A further object of the present invention is to provide compounds having improved anthelmintic activity. A still further object of the present invention is to provide further compounds having activity against parasitic nematodes. A yet further object of the present invention is to provide compounds having activity against parasitic trematodes and cestodes, many of which have hitherto been resistant to chemical control.

The present invention is directed to substituted quinoline derivatives having anthelmintic activity, pharmaceutical uses thereof and synthetic methods for their production.

In accordance with a first aspect of the invention, there is provided the use of a compound of Formula (I), (IA) or (IB):



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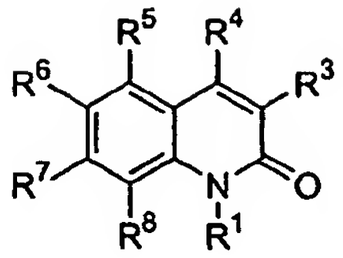

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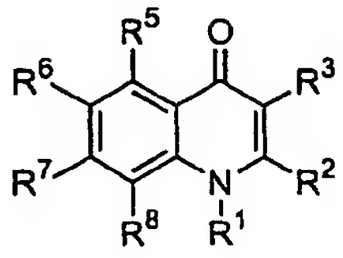


(IB)

in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of helminth infections, wherein:

R^1 represents H, C_1 to C_6 alkyl or benzyl;

R^2, R^3, R^4, R^5, R^6 R^7 and R^8 are each independently selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of: C_6 to C_{10} aryl, CN, F, Cl, Br, I, OH, SH, NO_2, OR^9, SR^9, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_{20} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_2 to C_{10} alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(v) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{15} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(vi) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(vii) a heterocyclic group which may be aromatic or non-aromatic having from 5 to 10 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen or sulfur atoms and the remainder are carbon atoms;

(viii) OR^{12};

(ix) a halo group selected from F, Cl, Br or I;

(x) $NR^{10}R^{11}$;

(xi) $COOR^{10}$;

(xii) NO_2;

(xiii) SR^{12};

(xiv) $CONR^{10}R^{11}$;

(xv) COR^9;

(xvi) CN;

(xvii) OH; or

(xviii) SH,

wherein:

R^9 represents C_1 to C_6 alkyl or C_6 to C_{15} aryl;

R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of hydrogen, C_1 to C_6 alkyl and C_6 to C_{15} aryl; and

R^{12} represents C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

or an N-oxide derivative thereof, wherein the quinoline ring nitrogen forms an N-oxide group, or a pharmaceutically acceptable salt, solvate or quaternary

ammonium salt thereof, with the proviso that (a) at least one of R^2 and R^4 is other than hydrogen and (b) for the compounds of Formula (IA) wherein R^3 represents dimethylallyl and R^4 represents ethoxy, at least one of R^5, R^6, R^7 and R^8 is other than hydrogen.

Preferably, in the compounds of Formula (I), (IA) or (IB) R^2 represents

(i) C_1 to C_6 alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, CN, F, Cl, Br, I, OH, SH, NO_2, OR^9, SR^9, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(ii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(iii) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(iv) OR^{12};

(v) a halo group selected from F, Cl, Br or I;

(vi) $NR^{10}R^{11}$;

(vii) $COOR^{10}$;

(viii) SR^{12};

(ix) $CONR^{10}R^{11}$;

(x) COR^9; or

(xi) CN

wherein R^9, R^{10}, R^{11} and R^{12} are as defined as above.

Particularly preferred R^2 groups are:

(i) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched;

(ii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, CF_3, OCF_3, OR^9 or SR^9;

(iii) OR^{12};

(iv) a halo group selected from F, Cl, Br or I;

(v) $COOR^{10}$; or

(vi) COR^9

wherein R^9, R^{10} and R^{12} are as defined as above.

Especially preferred are compounds of Formula (I), (IA) or (IB) wherein R^2 represents:

(i) OR^{12}, wherein R^{12} is as defined as above, and is preferably unsubstituted, branched or unbranched C_1 to C_6 alkyl; or

(ii) a halo group selected from F, Cl, Br or I.

In the compounds of Formula (I), (IA) or (IB), R^2 is preferably methoxy or halo.

Preferred groups for R^3 in the compounds of Formula (I), (IA) or (IB) are:

(i) hydrogen;

(ii) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, CN, F, Cl, Br, I, OH, SH, NO_2, OR^9, SR^9, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_{20} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(v) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_8 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(vi) OR^{12} wherein R^{12} represents C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2 and $NR^{10}R^{11}$ wherein R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of hydrogen, C_1 to C_6 alkyl and C_6 to C_{15} aryl; or

(vii) a halo group selected from F, Cl, Br or I,

wherein unless stated otherwise, R^9, R^{10}, R^{11} and R^{12} are as defined above.

More preferably R^3 represents:

(i) hydrogen;

(ii) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched

(iii) unsubstituted C_6 to C_{15} aryl;

(iv) OR^{12} wherein R^{12} represents C_1 to C_6 alkyl; or

(v) a halo group selected from F, Cl, Br, I.

Especially preferred compounds of Formula **(I)**, **(IA)** or **(IB)** are those wherein R^3 represents hydrogen or halo, and preferably hydrogen.

For the compounds of Formula **(I)**, **(IA)** or **(IB)**, R^4 is preferably selected from:

(i) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO^2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(ii) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(iii) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(iv) OR^{12} ~~wherein R^{12} represents C_1 to C_{20} alkyl,~~ which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(v) a halo group selected from F, Cl, Br or I;

(vi) $NR^{10}R^{11}$;

(vii) $COOR^{10}$;

(viii) SR^{12};

(ix) $CONR^{10}R^{11}$;

(x) COR^9; or

(xi) CN,

wherein R^9, R^{10}, R^{11} and R^{12} are as defined as above.

Preferred R^4 groups are selected from:

(i) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched;

(ii) unsubstituted C_6 to C_{10} aryl;

(iii) OR^{12};

(iv) a halo group selected from F, Cl, Br or I;

(v) $COOR^{10}$; and

(vi) COR^9,

wherein R^9, R^{10} and R^{12} are as defined as above.

Especially preferred are compounds of Formula (**I**), (**IA**) or (**IB**) wherein R^4 represents

(i) OR^{12} wherein R^{12} is as defined as above, and preferably R^{12} represents unsubstituted C_1 to C_6 alkyl, which may be branched, or unbranched; or

(ii) a halo group selected from F, Cl, Br or I.

Most preferred are compounds of Formula (I), (IA) or (IB) wherein R^4 represents methoxy or halo.

In preferred compounds of Formula (I), (IA) or (IB), R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, and $NR^{10}R^{11}$;

(iii) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(iv) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, CF_3, OCF_3 and $NR^{10}R^{11}$;

(v) a heterocyclic group having from 5 to 10 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen or sulfur atoms and the remainder are carbon atoms;

(vi) OR^{12};

(vii) a halo group selected from F, Cl, Br or I;

(viii) COR^9;

(ix) CN; and

(x) OH,

wherein R^9, R^{10}, R^{11} and R^{12} are as defined as above.

Further preferred compounds for use in the present invention are those wherein R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:

(i) hydrogen

(ii) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched;

(iii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CF_3 and OCF_3;

(iv) the group OR^{12}; and

(v) ~~a halo group~~ selected from F, Cl, Br and I.

Particularly preferred R^5, R^6, R^7 and R^8 groups are independently selected from the group consisting of:

(i) hydrogen

(ii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CF_3 and OCF_3; and

(iii) a halo group selected from F, Cl, Br or I.

Especially preferred are compounds of Formula (**I**), (**IA**) or (**IB**) wherein R^5, R^6, R^7 and R^8 are each independently selected from hydrogen, C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-3 alkoxy groups OR^9, wherein R^9 is as defined as above.

Particularly preferred compounds of Formula (**I**), (**IA**) or (**IB**) for use in the present invention are those wherein R^2 and R^4 both represents methoxy.

For the above compounds of Formula (**I**), (**IA**) or (**IB**), R^5 preferably represents

(i) hydrogen

(ii) C_1 to C_6 alkyl which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9 or a halo group selected from F, Cl, Br and I;

(iii) C_6 to C_{10} aryl which may be unsubstituted or substituted with 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9 F, Cl, Br, I, CF_3 and OCF_3; or

(iv) a halo group selected from F, Cl, Br and I.

Even more preferred R^5 groups are selected from hydrogen, unsubstituted C_1 to C_6 alkyl, or a halo group selected from F, Cl, Br and I. Preferably, in the compounds of Formula (I), (IA) or (IB), R^5 represents hydrogen.

In the compounds of Formula (I), (IA) or (IB) R^6 ~~preferably represents a~~ substituent selected from the group consisting of:

(i) hydrogen,

(ii) C_1 to C_6 alkyl which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of OR^9, SR^9, F, Cl, Br and I;

(iii) C_6 to C_{10} aryl which may be unsubstituted or substituted with 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, F, Cl, Br, I, CF_3 and OCF_3; and

(iv) a halo group selected from F, Cl, Br and I.

In preferred compounds of Formula (I), (IA) or (IB), R^7 represents hydrogen, unsubstituted C_1 to C_6 alkyl, or a halo group selected from F, Cl Br and I. Even more preferably, R^7 represents hydrogen.

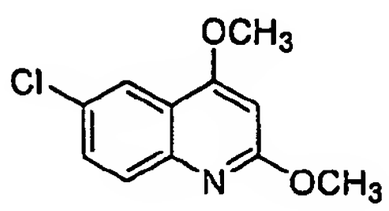
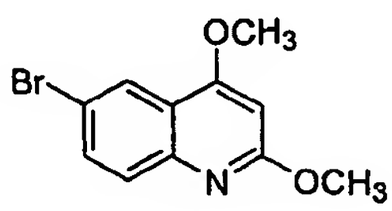
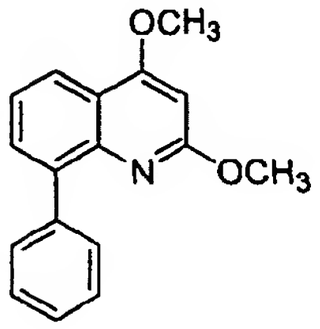
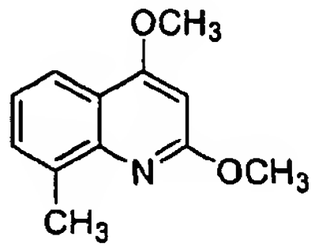
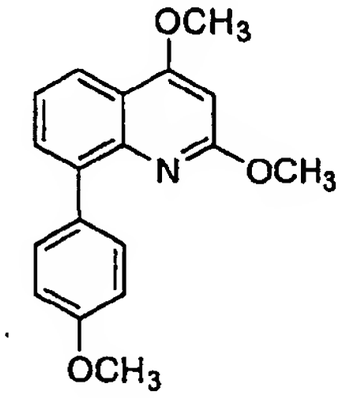
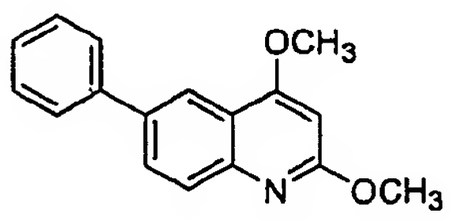
Also preferred compounds of Formula (I), (IA) or (IB) are those wherein one of R^5, R^6, R^7 and R^8 is other than hydrogen, and the remaining three represent hydrogen.

In preferred compounds of Formula (I), (IA) or (IB), R^9 represents unsubstituted C_1 to C_6 alkyl. Also, in preferred compounds of Formula (I), (IA) or (IB), R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of H and C_1 to C_6 alkyl. R^{12} preferably represents unsubstituted C_1 to C_6 alkyl.

Preferably, of the compounds of Formula (I), (IA) or (IB), the group R^{12} represents unsubstituted C_1 to C_6 alkyl.

Particularly preferred compounds of Formula (IA) or (IB) are those wherein R^1 represents H.

Especially preferred compounds for use in the present invention are those having the following structures: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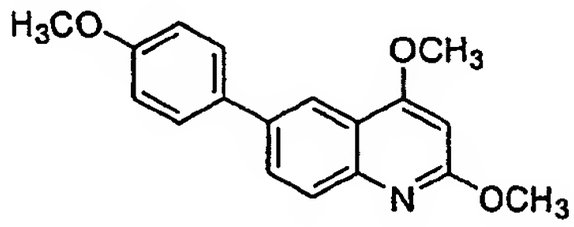
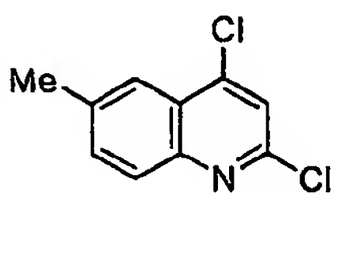
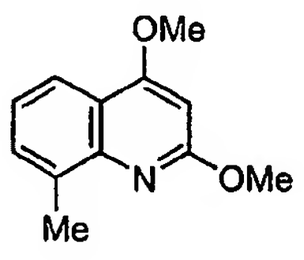


Further preferred compounds for use in the present invention are those having the following structures: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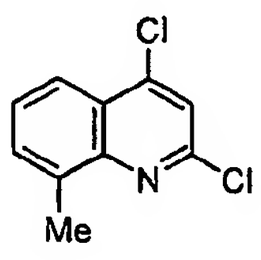
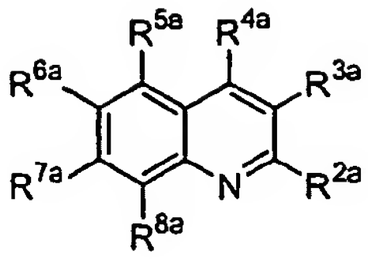
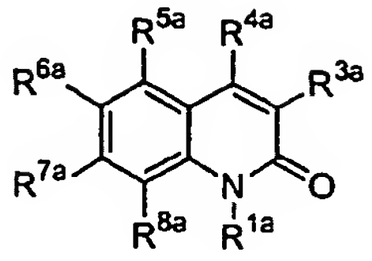


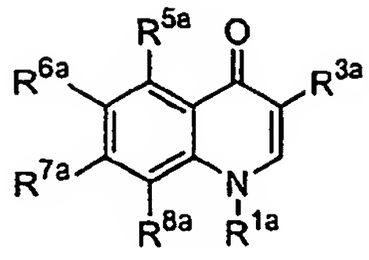
In a further aspect of the present invention, there is provided novel compounds of Formula (II), (IIA) or (IIB):



(II)



(IIA)



(IIB)

wherein:

R^{1a} represents H, C_1 to C_6 alkyl or benzyl

R^{2a} represents OR^{12} or SR^{12};

R^{4a} represents OR^{12} or SR^{12};

R^{3a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} is selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_{20} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_2 to C_{10} alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(v) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, $NR^{10}R^{11}$, $COOR^{10}$, COR^9, OCF_3 and CF_3;

(vi) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6

alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, OH, SH, NO_2, $NR^{10}R^{11}$, $COOR^{10}$, COR^9, OCF_3 and CF_3;

(vii) a heterocyclic group, which may be aromatic or non-aromatic, having from 5 to 10 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen or sulfur atoms and the remainder are carbon atoms;

(viii) OR^{12}; or

(ix) a halo group selected from F, Cl, Br or I;

with the proviso that at least one of R^{5a}, R^{6a}, R^{7a} and R^{8a} is selected from the group consisting of:

(i) C_2 to C_{10} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9 or SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(ii) C_2 to C_{10} alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, $NR^{10}R^{11}$, OCF_3 and CF_3;

(iv) the group OR^{12}; and

(v) a halo group selected from F, Cl, Br or I,

wherein R^9 represents C_1 to C_6 alkyl or C_6 to C_{15} aryl;

R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of hydrogen, C_1 to C_6 alkyl and C_6 to C_{15} aryl; and

R^{12} represents C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the

group consisting of OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

or an N-oxide derivative thereof, wherein the quinoline ring nitrogen forms an N-oxide group, or a pharmaceutically acceptable salt, or solvate, or addition salt or a quaternary ammonium salt thereof.

Preferably for the compounds of Formula (II), (IIA) or (IIB), R^{3a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are independently selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_6 alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9 or SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(v) OR^{12} wherein R^{12}; or

(vi) a halo group selected from F, Cl, Br and I,

wherein R^9, R^{10}, R^{11} and R^{12} are as defined as above.

Particularly preferred compound of Formula (II), (IIA) or (IIB) are those wherein R^{3a} represents hydrogen.

Further preferred compounds of Formula (II), (IIA) or (IIB) are those wherein R^{5a}, R^{6a}, R^{7a} and R^{8a} are selected from the group consisting of:

(i) hydrogen;

(ii) unsubstituted C_1 to C_6 alkyl which may be branched or unbranched;

(iii) unsubstituted C_1 to C_6 alkynyl, which may be branched or unbranched;

(iv) unsubstituted C_6 to C_{10} aryl;

(v) OR^{12}; and

(vi) a halo group selected from F, Cl, Br or I.

Even more preferred are compounds wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} is other than hydrogen and the remaining three represent hydrogen.

Of these compounds of Formula (II), (IIA) or (IIB), it is preferred that one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents a group selected from:

(i) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(ii) OR^{12}; and

(iii) a halo group selected from F, Cl or Br,

and the remaining three represent hydrogen, wherein R^9, R^{10}, R^{11} and R^{12} are as defined as above.

Especially preferred compounds are those wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, OCF_3, CF_3, F, Cl, Br and I; and the remaining three represent hydrogen.

Also preferred are compounds of Formula (II), (IIA) or (IIB) wherein at least one of R^{6a} and R^{8a} represents a group selected from: F, Cl, Br, I and OR^{12} wherein R^{12} as defined as above.

Further preferred are compounds of Formula (II), (IIA) or (IIB) wherein at least one of R^{6a} and R^{8a} is selected from phenyl which may be unsubstituted or

substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, F, Cl, Br, I, OCF_3, CF_3, OR^9 and SR^9 wherein R^9 represents C_1 to C_6 alkyl. Preferably, at least one of R^{6a} and R^{6a} is selected from phenyl which may be substituted by 1-3 methoxy groups.

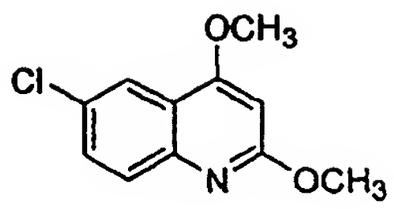
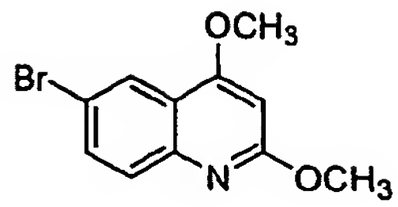
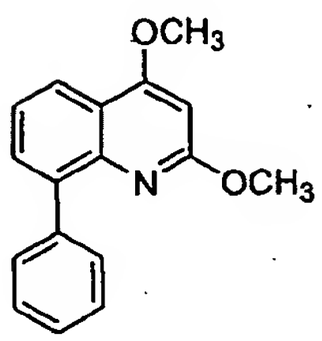
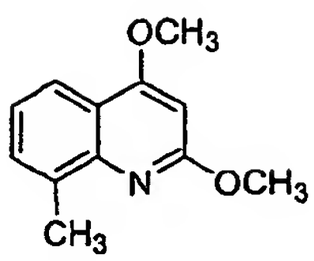
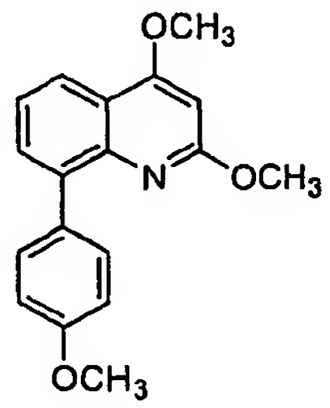
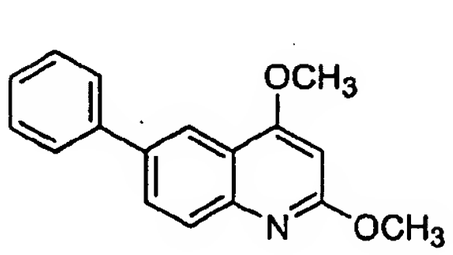
Of the compounds of Formula **(II)**, **(IIA)** or **(IIB)**, especially preferred are those wherein R^{5a} represents hydrogen.

Also, in preferred compounds of Formula **(II)**, **(IIA)** or **(IIB)**, R^{7a} represents hydrogen. Especially preferred are compounds of Formula **(II)**, **(IIA)** or **(IIB)** wherein both R^{5a} and R^{6a} represent hydrogen.

For the compounds of Formula **(II)**, **(IIA)** or **(IIB)**, R^9 preferably represents unsubstituted C_1 to C_6 alkyl. Preferably, R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of H and C_1 to C_6 alkyl.

Especially preferred compounds of Formula **(IIA)** or **(IIB)** are those wherein R^{1a} represents H.

Preferred novel compounds of the present invention include those having the following structures: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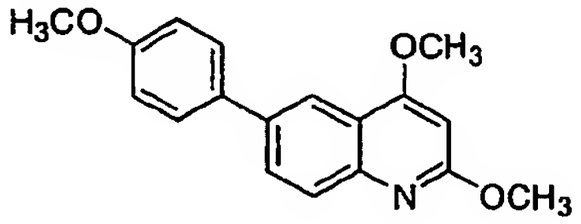
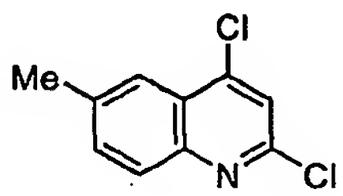
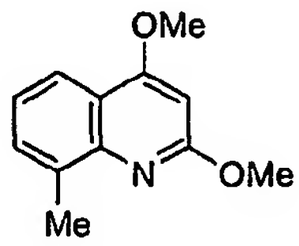


Further preferred novel compounds of the present invention include those selected from the group consisting of: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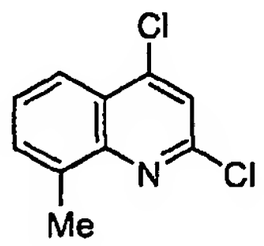


According to another aspect of the present invention there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Formula (II), (IIA) or (IIB) in a pharmaceutical carrier.

The compounds of Formula (I), (IA), (IB), (II), (IIA) and (IIB) are useful in the manufacture of a medicament for the treatment or prophylaxis of parasitic helminth infections, caused by nematodes, trematodes or cestodes, in humans and veterinary animals, particularly agricultural livestock including cattle, sheep, goats, pigs, equine and poultry. Such diseases include ascariasis, filariasis, loaiasis, onchocerciasis, schistosomiasis, trichinelliasis and hydatid disease.

Examples of parasitic nematodes include, but are not limited to, *Ostertagia lyrata, O. ostertagi, O. circumcincta, Cooperia oncophora, C. pectinata, C. punctata, C. surnabada, C. curticea, Haemonchus contortus, H. placei, Trichostrongylus axei, T. colubriformis, T. vetrinus, Bunostomum phlebotomum, B. trigonocephalum, Oesophagostomum radiatum, O. dentatum, O. venulosum, O. columbianum, Strongyloides papillosus, S. westeri, S. stercoralis, Nematodirus helvetianus, N. spathiger, N. filicolis, Trichuris spp., Strongylus vulgaris, S. edentatus, S. equinus, Triodontophorus spp., Oxyuris equi, Parascaris equorum, Habronema muscae, Oncocerca spp., Dirofilaria immitis, Toxocara canis, Toxascaris leonina, Ancylostoma caninum, A. braziliense, A. duodenale, Thelazia spp., Uncinaria stenocephala, Chaberia ovina, Ascaris lumbricoides, Dictyocaulus vivaparus, D. arnfieldi, D. filaria, Brugia malayi, B. timori, Dioctophyma renale, Enterobius vermicularis, Loa loa, Mansonella ozzardi, M. perstans, M. streptocerca, Necator americanus, Onchocerca volvulus, Stronglyloides stercoralis, Trichinella spiralis, T. triciura and Wuchereria bancrofti)*

Examples of plant-damaging nematodes include, but are not limited to, the following genera: *Meloidogyne, Heterodera, Ditylenchus, Aphelenchoides, Radopholus, Globodera, Pratylenchus, Longidorus* and *Xiphenema*.

Examples of parasitic cestodes include, but are not limited to: *Diphyllobothrium latum, D. caninum, Echinococcus granulosus, E. multilocularis, Hymenolepsis diminuta, Taenia multiceps, T. saginatus, T. serialis, T. solium and Vampirolepis nana*.

Examples of parasitic trematodes include, but are not limited to *Clonorchis sinensis, Dicrocoelium dendriticum, an echinostome, Fasciolopsis buski, Fasciola hepatica, a heterophyid, Nanophyetus salmincola, Opisthorchis felineus, O. viverrini, Paragonimus kellicotti, P. westermani, Schistosoma haematobium, S. japonicum, S. mansoni, S. intercalatum* and *S. mekongi*.

The compounds of the invention are also useful in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of infections of arthropod ectoparasites, such as flies, lice, keds, fleas, ticks, mites and certain copepod of fish. The activity of the compounds may be against all or individual development stages.

The compounds of the present invention are also particularly useful for the treatment or prophylaxis of infections caused by ticks, which include, but are not limited by *Boophilus* spp, *Rhipicephalus* spp, *Ixodes* spp, *Hyalomma* spp, *Amblyomma* spp, *Dermacentor* spp and *Argas* spp; mites, which include, but are not limited by *Psoroptes* spp, *Chorioptes* spp, *Sarcoptes* spp and *Demodex* spp; flies, which include, but are not limited by *Musca* spp, *Stomoxys* spp, *Oestrus* spp, *Culicoides* spp, *Tabanus* spp, *Phlebotomus* spp, *Simulium* spp, *Lucilia* spp, *Calliphora* spp, *Dermatobia* spp and *Hypoderma* spp; lice, which include, but are not limited by *Linognathus* spp, *Bovicola* spp, *Haematopinus* spp and *Solenopotes* spp; keds, such as *Melophagus ovinus*; fleas, which include, but are not limited by *Ctenocephalides* spp and ectoparasites of fish, such as the copepod parasites *Lepeophtheirus salmonis* and *Caligus elongatus*.

Formulations suitable for agricultural use include granules, pastes, sprays, powders, solutions and dusts. Formulation auxiliaries for such use include: solvents such as oils, alcohols, esters and water; carrier materials such as talc, kaolin, calcite, montmorillinite and attapulgite and dispersing agents.

The formulations may also contain further additives, such as stabilisers, antifoaming agents, viscosity regulators, binders and adhesives, as well as fertilisers or other active agents.

The compounds of Formula (I), (IA), (IB), (II), (IIA) and (IIB) may be administered to a vertebrate either alone, or preferably, in combination with pharmaceutically acceptable carriers or diluents, and optionally with known adjuvants. Such pharmaceutical compositions may comprise one or more

antiparasitic compounds of the invention. The compounds can be administered by oral, parenteral, intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, vaginal and topical routes of administration. The route of administration depends upon the site of the parasite infection and the mammal to be treated.

For administration to humans and animals, the compounds of the invention may be formulated in a variety of ways, depending upon biological and physicochemical parameters. Such formulations include, but are not limited by, tablets, chews, gels, pastes, granules, boluses, drenches, pour-ons, injectable suspensions or solutions, emulsions, solutions, water or oil dispersions, granules, microcapsules and waxes. Formulation auxiliaries including inert materials, surfactants, solvents and other additives known in the art may be suitably employed.

For example, the active compound may be administered by the oral route in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers that are commonly employed include lactose and cornstarch, and lubricating agents such as magnesium stearate, may be employed. For oral administration in capsule form, the formulation may comprise diluents such as lactose, starch, dried cornstarch, dicalcium phosphate. These unit dosage forms may be prepared by intimately and uniformly mixing the active ingredient with suitably finely divided diluents, fillers, disintegrating agents, and/or binders such as starch and vegetable gums. A particularly suitable mode of administration for the treatment of parasitic helminth infections of livestock is by the use of pellets or powders for adding to the animal feedstuff or drinking water.

The unit dosage formulations may be varied widely with respect to their total weight and content of the anthelmintic agent depending upon factors such as the host animal to be treated, the severity and type of infection and the weight of the host animal. For example, a composition for a single dose oral administration may comprise from 0.001 to 10, and preferably, 0.02 to 5 mg per kg of animal body weight. The compositions of the invention are also suitable for administration in a

controlled release dosage form. Such dosage forms are particularly useful for administering to agricultural livestock because of the requirement for repeated therapeutic treatment in such animals due to the likelihood of the re-exposure of the animals to the parasite.

Where aqueous suspensions are employed, the active compound may be combined with known emulsifying and suspending agents and stabilisers. For parenteral administration, the active compound may be dissolved or dispersed in a carrier vehicle, such as a vegetable oil, glycerol formal or water. Such compositions suitably comprise 0.005 to 30%, preferably 0.005 to 5% by weight, of the active agent.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds may be formulated into sterile solutions and the pH of the solution controlled as necessary with buffers. For intravenous use, the total concentration of the solutes should be controlled in order to render the preparation isotonic.

The compounds of the invention may also be prepared as a drench. The drench is normally a solution, suspension or dispersion of the active ingredient, and is usually aqueous. The drench may contain a suspending agent such as bentonite and a wetting agent or a similar excipient, and may further contain an antifoaming agent. Preferably, drench formulations comprise 0.001% to 10%, and more preferably, 0.01 to 5% by weight of the active agent.

The compounds of the invention may also be used as prophylactic agents. Prophylactic use of an antiparasitic agent is based on the epidemiology of the parasite. For example, a treatment regime comprising administering the active agent to agricultural livestock or plants at strategic times of the year may be advantageous in preventing infection.

Administration of the compounds to treat plant nematode infections may be carried out by spraying a solution of one or more of the active compounds on the

plant, or by introducing pellets or powder containing the active agent(s) into the soil.

The compounds of the invention may also be used in the manufacture of a medicament for use in treating parasitic helminth infections in animals comprising a further pharmaceutically active agent, including other known anthelmintics and immunomodulators, such as levamisole. A particularly useful pharmaceutical agent for use in combination with the compounds of the invention is a laxative, which may be useful in assisting the elimination of the parasites from the body.

As used herein, the following terms are used as defined below, unless otherwise indicated.

"Alkyl" represents straight or branched carbon chains, containing 1-20 carbon atoms, preferably 1-6 carbon atoms (for example, methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, isopentyl and hexyl). The term "alkyl" also includes straight or branched carbon chains, containing 1-20, and preferably 1-6 carbon atoms and which are substituted with 1-3 substituents independently selected from the group consisting of: C_1 to C_6 aryl, CN, F, Cl, Br, I, OH, SH, NO_2, OR^9, SR^9, COR^9, CO_2R^{10} and $NR^{10}R^{11}$ wherein R^9 represents C_1 to C_6 alkyl or C_6 to C_{15} aryl, and R^{10} and R^{11} may be the same or different and each is independently selected from the group consisting of H, C_1 to C_6 alkyl and C_6 to C_{15} aryl. Representative examples of substituted alkyl groups include $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CF_3$, $-(CH_2)_3OH$, and $-(CH_2)_2OR^9$. Particularly preferred are substituents for alkyl groups are selected from CN, F, Cl, OR^9 and $NR^{10}R^{11}$. In preferred embodiments of the invention, the term "alkyl" represents unsubstituted C_1-C_6 carbon chains.

"Alkenyl" represents straight or branched carbon chains having at least one carbon-carbon double bond and containing 2-20 carbon atoms, preferably 2-10 carbon atoms, and more preferably 2-6 carbon atoms. The term alkenyl also includes straight or branched carbon chains having at least one carbon-carbon double bond and containing 2-20, preferably 2-10 and more preferably 2-6 carbon atoms and which are substituted with 1-3 substituents independently selected

from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, CO_2R^{10} and $NR^{10}R^{11}$ wherein R^9 represents C_1 to C_6 alkyl and or C_6 to C_{15} aryl, and R^{10} and R^{11} may be the same or different and each is independently selected from the group consisting of H, C_1 to C_6 alkyl and C_6 to C_{15} aryl. Representative examples of substituted alkenyl groups include —CH=CHF, $-CF=CCl_2$, $-(CH_3)C=CF_2$ and $-(HO)CH=CH(CH_2CH_3)$. Preferably, the term "alkenyl" refers to unsubstituted straight or branched carbon chains having one carbon-carbon double bond, representative examples of which include $-CH=CH_2$, $-C(CH_3)=CHCH_3$ and $-CH_2CH=C(CH_3)_2$.

The term "alkynyl" represents straight or branched carbon chains having at least one carbon-carbon triple bond and containing from 2-10 carbon atoms, preferably 2-6 carbon atoms, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, CO_2R^{10} and $NR^{10}R^{11}$, wherein R^9 represents C_1 to C_6 alkyl and or C_6 to C_{15} aryl, and R^{10} and R^{11} may be the same or different and each is independently selected from the group consisting of H, C_1 to C_6 alkyl and C_6 to C_{15} aryl. Preferably, the substituents are selected from the group consisting of CN, F, Br, Cl, I, OH, OR^9 and SR^9, wherein R^9 represents C_1 to C_3 alkyl or halo. Particularly preferred substituents are selected from OR^9, F and Cl, wherein R^9 represents C_1 to C_3 alkyl (preferably methyl). Representative examples of substituted alkynyl groups include $-CH(CH_3)CF_2CH_2{\equiv}CH$ and $-CH(CH_3)CH(OMe)CH_2C{\equiv}H$, Preferably, the term "alkynyl" refers to unsubstituted C_2 to C_6 carbon chains which may be branched or unbranched, including $-C{\equiv}CH$, $-CH_2CH_2C{\equiv}CH$, $-CH_2CH(CH_3)CH_2C{\equiv}H$.

"Aryl" represents a carbocyclic group containing 6-15, preferably 6 to 10, carbon atoms and having at least one aromatic ring, and which may be substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_6 aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, CO_2R^{10}, OCF_3, CF_3 and $NR^{10}R^{11}$, wherein R^9 represents C_1 to C_6 alkyl and or C_6 to C_{15} aryl, and R^{10} and R^{11} may be the same or different and each is independently selected from the group

consisting of H, C_1 to C_6 alkyl and C_6 to C_{15} aryl. Preferably, the term "aryl" refers to a carbocyclic group containing 6-10 carbon atoms and which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl (such as phenyl), OR^9 and halo (F, Cl, Br and I), wherein R^9 represents ~~unsubstituted C_1 to C_6~~ alkyl. In particularly preferred embodiments of the invention, the term "aryl" refers to phenyl substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_3 alkyl and OR^9, wherein R^9 represents C_1 to C_3 alkyl. In especially preferred embodiments of the invention, the term "aryl" refers to phenyl substituted by 1-3 substituents independently selected from C_1 to C_3 alkyl (preferably CH_3) or OR^9 wherein R^9 represents C_1 to C_3 alkyl (preferably methyl).

"Cycloalkyl" represents a carbocyclic group containing from 3-8 carbon atoms forming at least one saturated ring, and which may be unsubstituted or substituted by 1-5 substituents on the ring carbon atoms, the substituents being independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, OCF_3, CF_3, CO_2R^{10} and $NR^{10}R^{11}$ wherein R^9 represents C_1 to C_6 alkyl and or C_6 to C_{15} aryl, and R^{10} and R^{11} may be the same or different and each is independently selected from the group consisting of H, C_1 to C_6 alkyl and C_6 to C_{15} aryl. For substituted cycloalkyl groups, particularly preferred substituents are selected from the group consisting of C_1 to C_3 alkyl, C_6 to C_{10} aryl, OR^9 (wherein R^9 represents C_1 to C_3 alkyl) and halo (F, Cl, Br). Particularly preferred compounds are those wherein the term "cycloalkyl" represents cyclopentyl or cyclohexyl, which may be unsubstituted or substituted with the above groups.

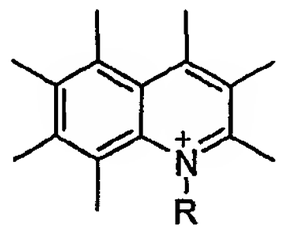
The term "heterocyclic group" refers to an aromatic (heteroaryl) or heterocycloalkyl group having from 5 to 10 ring atoms wherein 1, 2 or 3 of the ring atoms are independently selected from nitrogen, oxygen or sulfur atoms and the remainder are carbon atoms, wherein any one of the ring atoms is a point of attachment. Preferred heteroaromatic groups include pyridyl, thiazolyl, thiophenyl, furanyl, benzotriazolyl, quinolyl, isoquinolyl, pyrimidinyl, pyrrolyl, oxazolyl, indolyl and

Imidazolyl. Especially preferred heteroaromatic groups include pyridyl, thiazolyl, thiophenyl, furanyl, indolyl and imidazolyl. Representative non-aromatic heterocyclic substituents include piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrofuranyl, 2- or 4-dioxanyl and 1-, 2- or 3-morpholino.

Unless otherwised indicated as being substituted, the terms "alkyl", "alkenyl", "alkynyl", "aryl", "cycloalkyl" and "heterocyclic group" refer to unsubstituted groups.

The term "halo" represents F, Cl, Br or I.

The term "quarternary ammonium salt" in the context of quinoline rings refers to compounds wherein the nitrogen atom of the quinoline ring is alkylated , e.g. with and alkyl halide, R-X, to form an N-alkylated analogue:



The term "N-oxide" refers to compounds wherein the nitrogen atom of the quinoline ring forms an N→O group.

Bonds drawn into the ring systems indicate that the indicated bond may be attached to any of the available substitutable ring atoms.

Certain compounds of the invention may exist in different isomeric (e.g. enantiomers and diastereoisomers) forms. The present invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms and other tautomeric forms are also included. It will be appreciated, for example, that for compounds wherein the carbon atoms of the quinoline 2- or 4-positions are directly bonded to an oxygen atom to form the group C=O (i.e. a quinolin-2-one or a quinolin-4-one), the quinolin-2-one or quinolin-4-one co-exists with the tautomeric 2- and 4-hydroxyquinoline, respectively:

or

Usually, for the 2-hydroxyquinolines, the quinolinone form is thermodynamically favoured, whereas for the 4-hydroxyquinolines, the quinolinol form is favoured.

Certain compounds will be acidic in nature, such as those compounds that possess a carboxyl or a phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminium, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines including as ammonia, alkyl amines, hydroxyalkylamines and N-methylglucamine.

It will be appreciated that basic compounds can also form pharmaceutically acceptable salts, such as acid addition salts. For example, the quinoline nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups may also form salts with weaker acids. Examples of suitable acids for salt formation include hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known in the art.

Methods of preparation of acid addition salts will be apparent to those skilled in the art. For example, the salts may be prepared by contacting the free base form with a sufficient amount, e.g. a stoichoimetric amount, of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution, such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium

bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base forms are otherwise equivalent to their respective free base forms for the purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for the purposes of the invention.

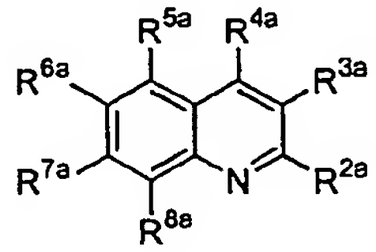
The compounds for use in the present invention may be synthesised by methods of quinoline synthesis known in the art, (see for example, Cheng, Y. Org. React. 1982, 28, 37-201 and Jones, G. in "Comprehensive Heterocyclic Chemistry II"; Katritzky, A.R., Rees, C.W. and Scriven, E.F.V., Eds., Pergamon, Oxford, 1996, Vol. 5, pp 167-243, and references cited therein.

A wide range of methods are known for the construction of the quinoline nucleus to form compounds useful in the present invention. Examples of synthetic routes to produce substituted quinolines will be apparent to a person of skill in the art. These include the Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses.

Substituted quinoline derivatives can be formed from an appropriately substituted aniline starting material. In a typical procedure, a two- or three- carbon fragment is condensed onto the nitrogen atom of the aniline. A subsequent cyclisation reaction step forms the quinoline ring. This procedure has wide applicability to the formation of substituted quinoline derivatives. For example, *ortho*- and *para*-substituted anilines may be used to produce 8- and 6-substituted quinolines, respectively; *meta*-substituted anilines give mixtures of 5- and 7-substituted quinolines. Where mixtures of positional isomers are formed, these may be separated by, for example, chromatographic procedures such as flash chromatography and HPLC.

A wide range of substituted aniline compounds suitable for use in the above synthesis of substituted quinolines are commercially available. The commercially available substituted anilines can also be derivatised to form the appropriate aniline derivative for use in the above synthesis. Substituted anilines for use in the above process may also be synthesised by procedures known in the art.

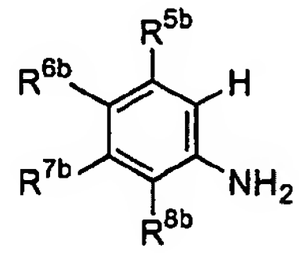
According to a further aspect of the present invention, there is provided process for the production of a compound of Formula (II):



(II)

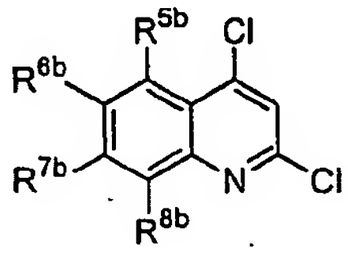
or an intermediate thereof, wherein R^{2a} and R^{4a} represent OR^{12} or SR^{12}; R^{12} represents C_1 to C_6 alkyl; and R^{3a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are as defined as above and are other than C_2 to C_{10} alkenyl, C_2 to C_{10} alkynyl, or C_6 to C_{15} aryl, comprising the steps of:

(a) subjecting a compound of Formula (III)



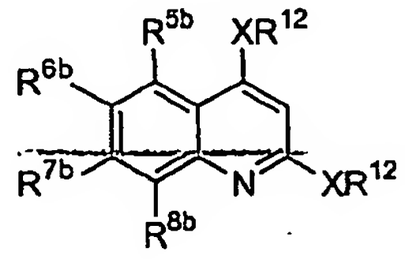
(III)

wherein R^{5b}, R^{6b}, R^{7b} and R^{8b} respectively represent the groups R^{5a}, R^{6a}, R^{7a} and R^{8a} or precursors thereof, to reaction with malonic acid in the presence of phosphorus oxychloride to produce a compound of Formula (IV):



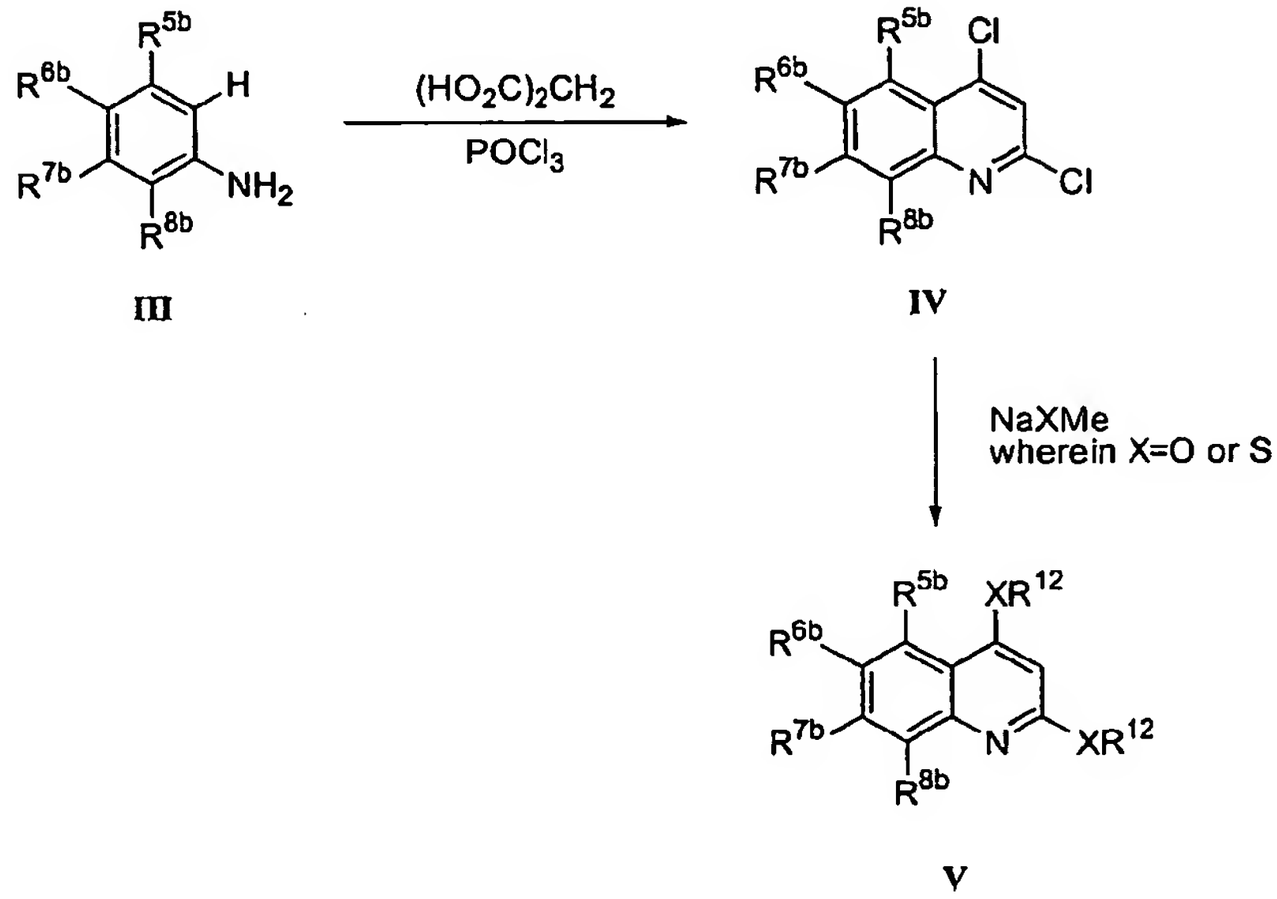
(IV) ; and

(b) subjecting the compound of Formula (IV) to reaction with $NaXR^{12}$, wherein X represents oxygen or sulphur to form a compound of Formula (V):



(V)

The process is illustrated in the following scheme:



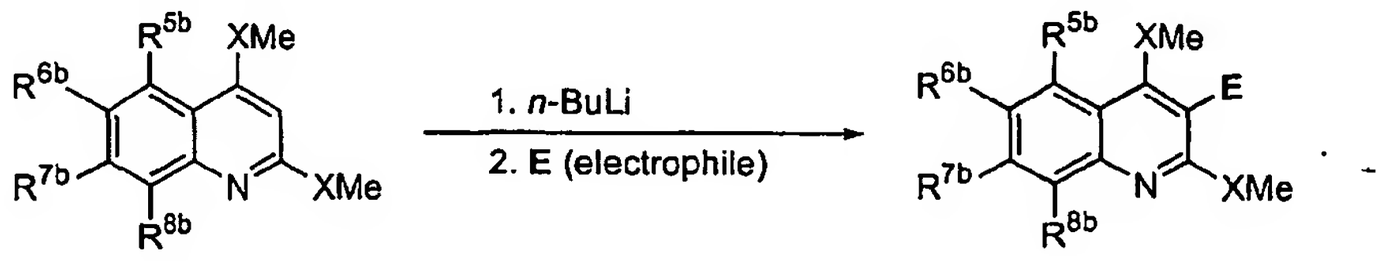
III IV V

Preferably, step (a) is carried out using neat reagents, i.e. in the absence of solvent. Thus, in a typical procedure, the compound of Formula (III) is heated with an excess of malonic acid and phosphorus oxychloride under reflux. In some cases, mixtures of positional isomers of the quinolines may be formed, depending on the substitution pattern of the aniline starting material. Such mixtures may be separated after step (a) by conventional chromatographic techniques, e.g. by column chromatography. Alternatively step (b) may be carried out using the mixture of quinoline isomers from step (a), and the separation step carried out subsequently.

In the above process, R^{5b}, R^{6b}, R^{7b} and R^{8b} respectively represent precursors to the groups R^{5a}, R^{6a}, R^{7a} and R^{8a}. Alternatively, the groups R^{5b}, R^{6b}, R^{7b} and R^{8b} can be protected groups corresponding to R^{5a}, R^{6a}, R^{7a} and R^{8a} or precursors thereof. Suitable protecting groups are well known in the art (see e.g. "Protective Groups in Organic Synthesis", Greene, T.W., Witts, P.G.M., John Wiley, N.Y. 1999). The precursors or protected intermediates may be subsequently converted to the respective substituents R^{5a}, R^{6a}, R^{7a} and R^{8a} by known procedures (see Comins, D.L and Joseph, S.P. in "Comprehensive Heterocyclic Chemistry II"; Katritzky, A.R., Rees, C.W. and Scriven, E.F.V., Eds. Pergamon, Oxford, 1996, Vol. 5, pp 167-243 and Dennis, N. in "Comprehensive Heterocyclic Chemistry II"; Katritzky, A.R., Rees, C.W. and Scriven, E.F.V., Eds. Pergamon, Oxford, 1996, Vol. 5, pp 91-134, and references cited therein).

In a typical procedure for step (b) of the above process, the substituted quinoline, or mixture of substituted quinoline isomers from step (a) is heated with the compound $NaXR^{12}$ under reflux. Where a mixture of substituted quinoline starting materials is used, the mixture from step (b) may be separated using standard chromatographic techniques.

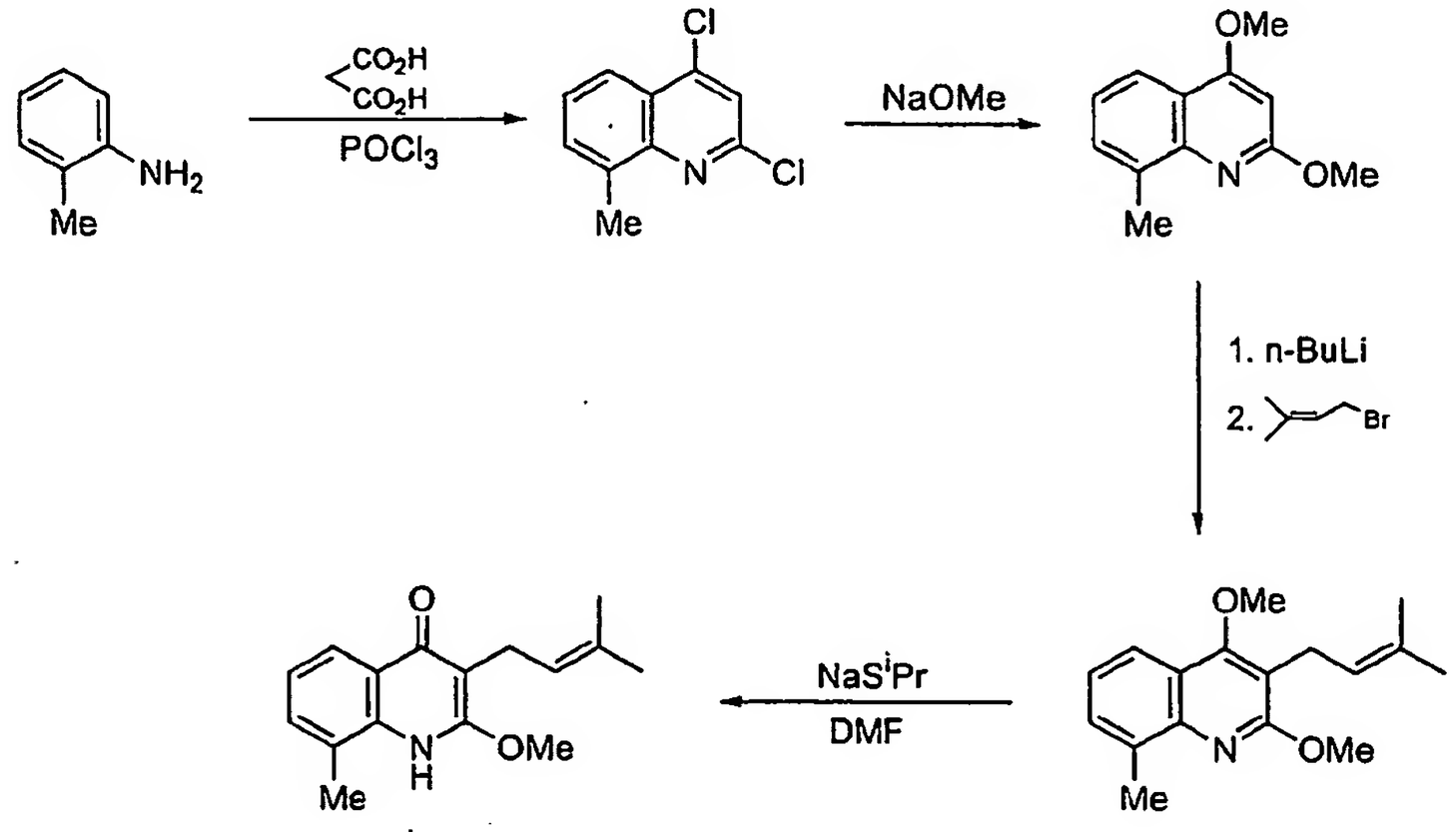
In the above process, the compounds of Formula (**II**) that are substituted in the quinoline 3-position (i.e. R^{3a} is other than hydrogen), may be produced by a subsequent reaction step comprising subjecting the compound of Formula (**V**) to a deprotonation reaction at the quinoline 3-position using a strong base, such as an alkyllithium, and quenching the anion with an electrophile to form the group R^{3a} or a precursor thereof:



Suitable electrophiles for the above reaction include ketones, aldehydes, halogens, halogen-producing agents (such as 1,2-dibromotetrafluoroethane),

pseudohalogens (such as phenylthio compounds) and epoxides. The 3-substituted compounds may be further derivatised to form further compounds of Formula (II), (IIA) or (IIB).

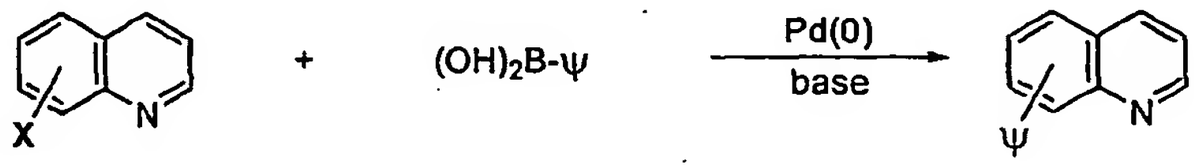
It will be apparent from the above that a variety of methods known in the art may be suitable for producing substituted quinoline derivative useful in the present invention. As a illustrative example, the synthesis of a 2,4,8-trisubstituted quinoline is shown in the following scheme:



According to a still further aspect of the present invention, there is provided a process for producing a compound of Formula (II) or an intermediate thereof, wherein at least one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents a substituent selected from substituted or unsubstituted C_2 to C_{10} alkenyl, substituted or unsubstituted C_2 to C_{10} alkynyl, or substituted or unsubstituted C_6 to C_{15} aryl wherein the substituents are as defined above, comprising reacting a compound of Formula (II) wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents Br, I or triflate with a boronic acid derivative of Formula (VI):

$$(OH)_2B\text{-}\psi \qquad (VI)$$

wherein ψ represents a substituted or unsubstituted C_2 to C_{10} alkenyl, substituted or unsubstituted C_2 to C_{10} alkynyl, substituted or unsubstituted C_6 to C_{15} aryl or substituted or unsubstituted C_5 to C_{10} heteroaryl group as defined above; in the presence of a base and a palladium or nickel catalyst under Suzuki coupling conditions. The reaction may be represented thus:



X = Cl, Br, I or OSO_2CF_3

ψ = unsubstituted or substituted aryl, alkenyl or alkynyl

Thus, as indicated above, the appropriate quinolyl bromide, iodide or triflate is reacted with a boronic acid in the presence of a palladium (0) catalyst and a suitable base to form the substituted quinoline derivatives of the invention wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents a C_2 to C_{10} alkenyl, C_2 to C_{10} alkynyl or C_6 to C_{15} aryl group, since a large number of aryl, alkenyl, alkynyl and heteroaryl boronic acids are commercially available or can be readily synthesised [see Lancaster Synthesis Catalogue 2000-2001, Appendix 5, pp. A39-A46, and references cited therein, Stanforth, S.P., Tetrahedron, (1998), 54, 263; Ishiyama, T., Murata, M., Miyaura, N., J. Org. Chem. (1995), 60, 7508].

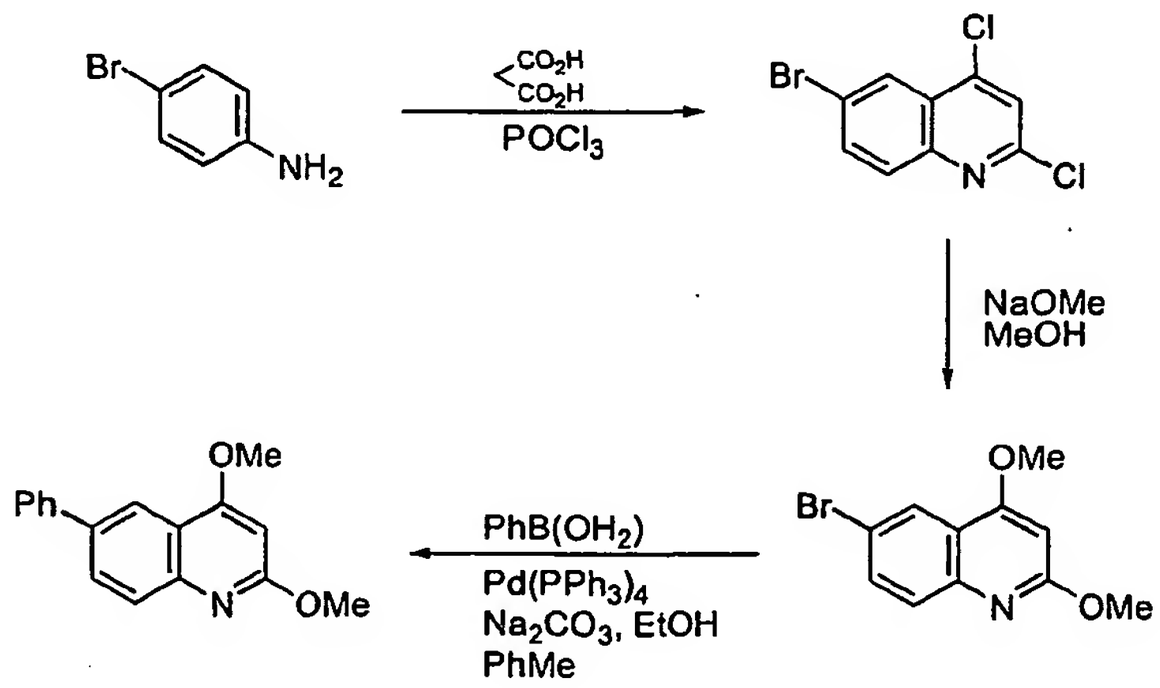
Suitable catalysts for this process include the following: $Pd(PPh_3)_4$, $Ni(dppf)Cl_2$ $Pd(dba)_2$ (dba = dibenzilidene acetone), $Pd(OAc)_2$, $Pd(OAc)_2/(o\text{-}tol)_3P$ [$(o\text{-}tol)_3Ph$ = tri(o-tolyl)phosphine], $Pd(OAc)_2$/dppf [dppf = 1,1'-bis(diphenylphosphino)-ferrocene] , $(PhCN_2PdCl_2/Ph_3As$ (Ph_3As = triphenyl arsine), $(CH_3CN)_2PdCl_2$, Pd-C, $(Ph_3P)_2NiCl_2$, $Pd(dppb)Cl_2$, bis(tricyclohexylphosphine)palladium(II) chloride, $(Ph_3P)_2PdCl_2$ and trans-di-μ-acetatobis[2-(di-o-tolylphosphino)benzyl]-dipalladium(II) (see Appendix 5, page A41, Lancaster Synthesis Catalogue 2000-2001, and references cited therein). Particularly preferred are palladium catalysts comprising phosphine ligands, such as $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$. These catalysts are suitable for high reaction temperatures because of their

stability. Alternatively, phosphine-free catalysts such as palladium acetate may be used, and advantageously, can give a more rapid conversion.

Suitable bases for the Suzuki coupling reaction include sodium carbonate, $NaHCO_3$, K_2CO_3, Cs_2CO_3, K_3PO_4, Et_3N, Ag_2O, $Ba(OH)_2$ and CsF. Sodium carbonate is a particularly preferred base.

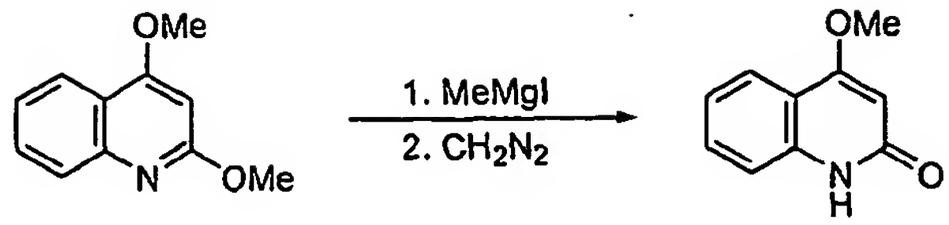
Typically the reaction is carried out in an inert solvent comprising a hydrocarbon, such as benzene or toluene. Preferably, the reaction is carried in the presence of a solvent containing water.

As an illustrative example, the synthetic route to form 2,4-dimethoxy-6-phenylquinoline is shown below:

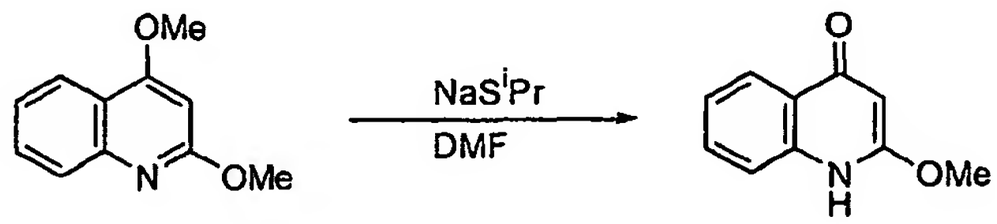


Compounds wherein the 2-position of the quinoline ring represents the group =O, i.e. substituted quinolinones of Formula (IIA), can be produced, for example, from the corresponding 2-alkoxy derivative by reaction with trimethylsilyl iodide.

Alternatively, quinolin-2-one derivatives can be produced from the corresponding 2,4-dimethoxy derivatives by a two step reaction procedure comprising (a) cleavage of both methoxy groups using a Grignard reagent, such as MeMgI, followed by (b) methylation at the 4-position to reinstall the methoxy group:



Substituted quinolin-4-ones corresponding to Formula (**IIB**) may be produced by treatment of the corresponding 2,4-dimethoxyquinoline derivative with sodium isopropyl thiolate in DMF, resulting in the selective demethylation of the 4-methoxy group:



N-oxide derivatives of the compounds of the present invention may be formed by methods of quinoline N-oxidation known in the art. As an example, a substituted quinoline intermediate or final compound may be treated with hydrogen peroxide or peracids, such as meta-chloroperoxybenzoic acid (MCPBA) to form the corresponding substituted quinoline-N-oxide analogue.

Compounds of Formula (**IIA**) or (**IIB**) wherein R^{1a} represents a C_1 to C_6 alkyl group or a benzyl group, may be formed by reaction of the corresponding substituted quinoline or intermediate thereof, wherein R^1 represents hydrogen, with suitable alkylating agents, e.g. alkyliodides or benzyl iodide by procedures known in the art.

EXAMPLES

The following Examples 1 to 72 illustrate the preparation of various quinoline derivatives of Formulae (I), (IA), (IB), (II), (IIA) or (IIB) and intermediates useful in the preparation of compounds of the invention. The procedures described for synthesising known compounds may be adapted for the preparation of compounds according to the invention by an appropriate selection of substituents and procedures for functional group conversions known in the art. Thus, Examples 1 and 2 illustrate procedures for the synthesis of substituted aniline intermediates useful for producing the compounds of the invention. Examples 3 to 19 illustrate the synthesis of known compounds useful in the invention and Examples 20 to 72 illustrate procedures for synthesising novel compounds of Formula (II), (IIA) and (IIB).

General experimental conditions

All moisture or oxygen sensitive reactions were carried out under argon. All glassware, syringes and needles were predried in an oven (110°C) and cooled in an anhydrous atmosphere prior to use. Organic phases were dried with magnesium sulfate or sodium carbonate.

Diethyl ether, tetrahydrofuran (THF), diisopropyl ether and toluene were distilled from sodium with benzophenone ketyl as indicator immediately before use. Dichloromethane was refluxed over calcium hydride and distilled directly into the reaction vessel. Dimethylformamide was heated to reflux over calcium hydride, distilled and stored over activated 3Å molecular sieves prior to use. Sodium hydride was washed with hexane before use.

Purification was carried out by flash column chromatography using Merck 7734 or Merck 60 (230-400 mesh) silica gel.

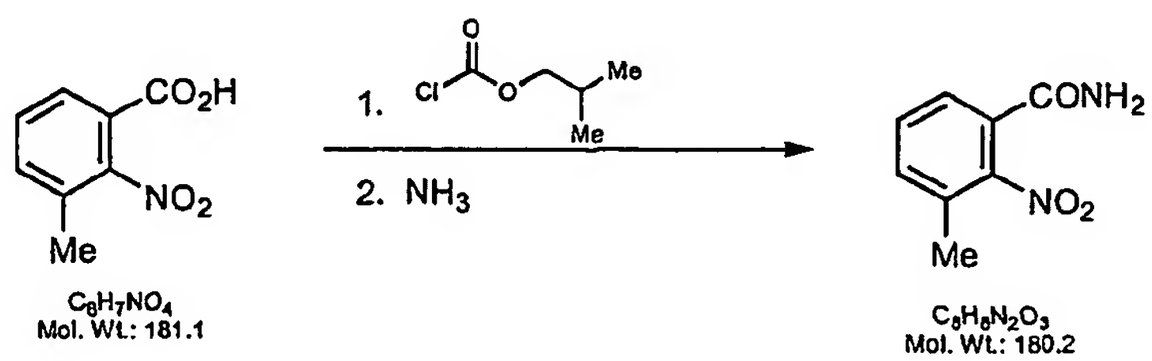
All melting points were determined on a Gallenkamp or Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin

Elmer Paragon 1000 FT-IR spectrophotometer using NaCl plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM360 spectrometer operating at 360 MHz for proton and 90 MHz for carbon. NMR spectra were recorded in deuteriochloroform ($CDCl_3$) as solvent, unless otherwise stated.

Tetramethylsilane (TMS) was adopted as the internal standard for ^{1}H NMR spectra and the solvent peaks were adopted as the internal standard for ^{13}C NMR spectra . Chemical shifts (δ_H and δ_C) are quoted as parts per million downfield from tetramethylsilane. The multiplicity of a ^{1}H NMR signal is designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet. Coupling constants (*J*) are expressed in Hertz.

Mass spectra were recorded on either a Kratos MS89MS with Kratos DS90 software or a Jeol AX505W with Jeol complement data system. Samples were ionised electronically (EI), with an accelerating voltage of [a]6 kV. Analytical data are presented as ±0.01%..

EXAMPLE 1. 3-Methyl-2-nitrobenzamide



$C_8H_7NO_4$
Mol. Wt: 181.1

$C_8H_8N_2O_3$
Mol. Wt: 180.2

A mixture of 3-methyl-2-nitrobenzoic acid (3.0 g, 17 mmol) and triethylamine (1.7g, 17 mmol) in THF (50 ml) was cooled to 0°C. Isobutyl chloroformate (2.3 g, 17 mmol) was added, and the mixture stirred at 0°C for 5 minutes, then allowed to warm to room temperature and stirred for a further 2 hours. Concentrated ammonia solution (30 ml of 35% ammonia) was then added in one portion, and the mixture stirred overnight. The flask contents were transferred to a separating funnel, water (30 ml) was added, and the aqueous layer extracted with ethyl

acetate (2 x 30 ml). The combined organic layers were dried with $MgSO_4$, and the solvent removed under reduced pressure to give the crude product as a cream solid. Recrystallisation (EtOH) gave the product as cream needles, R_f (EtOAc) 0.56. Yield 2.4 g, 78%. Melting point 188-190°C.

Found M^+: 180.0531. $C_8H_8N_2O_3$ requires 180.0535.

δ_H (DMSO d_6): 8.20 (1H, br s, NH), 7.69 (1H, br s, NH), 7.60-7.52 (3H, m, Ar-H), 2.28 (3H, s, Me).

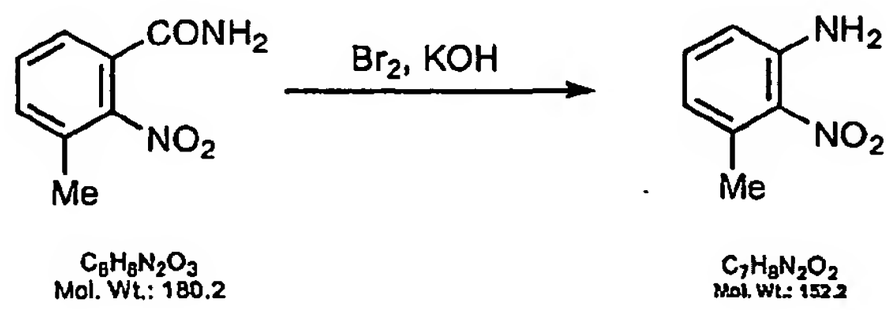
δ_C (DMSO d_6): 166.1 (C=O), 149.1 (C-NO_2) 133.5 (CH), 130.3 (CH), 129.9, 129.4, 126.2 (CH), 16.6 (Me).

n_{max} /cm^{-1}: 3337, 3183 (w, N-H), 1688 (s, C=O), 1525 (s, N=O).

m/z: 180 (80%, M^+), 164 (100%, $M^+ - NH_2$), 134 (17%, $M^+ - NO_2$), 89 (63%).

EXAMPLE 2. 3-Methyl-2-nitroaniline

Method A - by Hofmann rearrangement



$C_8H_8N_2O_3$
Mol. Wt.: 180.2

$C_7H_8N_2O_2$
Mol. Wt.: 152.2

Bromine (1.8 g, 11 mmol) was added to an ice-cold solution of potassium hydroxide (3.1 g, 55 mmol) in water (40 ml), and the resultant yellow solution stirred at 0°C for 10 minutes. 3-Methyl-2-nitrobenzamide (2.0 g, 11 mmol) was added in one portion, and the mixture heated at 65°C for 2 hours. After cooling, the product, a yellow precipitate, was filtered off and dried. The filtrate was extracted with ethyl acetate (3 x 30 ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give more of the product. Total yield 0.60 g, 36%. Melting point 103-105°C.

Found M^+: 152.0583. $C_7H_8N_2O_2$ requires 152.0586.

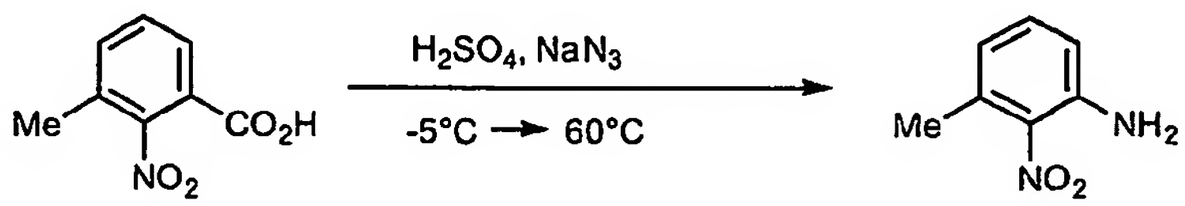
δ_H: 7.14 (1H, dd, *J* 8.2, 7.3, H5), 6.65 (1H, d, *J* 8.2, C4), 6.58 (1H, d, *J* 7.3, C6), 5.17 (2H, br s, NH_2), 2.46 (3H, s, Me).

δ_C: 143.3, 135.5, 135.5 (C-NH_2, CNO_2, CMe), 133.2 (C5), 121.1 (C4), 116.5 (C6), 21.4 (Me).

n_{max}/cm^{-1}: 3490, 3376 (w, N-H), 1610, 1584, 1552 (s, C=C, C=N, N=O).

m/z: 152 (98%, M^+), 135 (100%, M^+ - OH), 106 (36%, M^+ - NO_2), 77 (66%, $C_6H_5^+$).

Method B - by Schmidt rearrangement



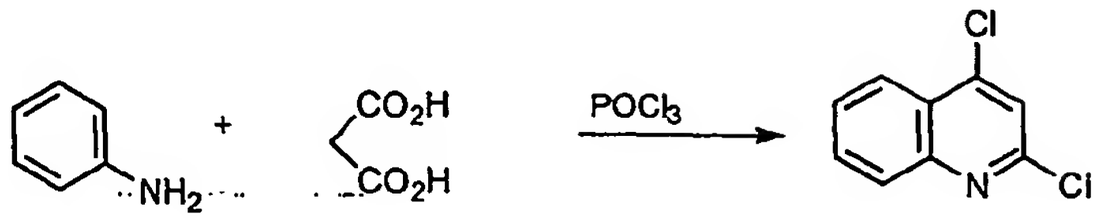
$C_8H_7NO_4$
Mol. Wt.: 181.1

$C_7H_8N_2O_2$
Mol. Wt.: 152.2

3-Methyl-2-nitrobenzoic acid (5.0 g, 28 mmol) was suspended in concentrated sulfuric acid (50 ml) and cooled to -5°C, with stirring. Sodium azide (1.8 g, 28 mmol) was added in small portions over 10 minutes, and the resulting deep violet mixture stirred at -5°C for 20 minutes and then allowed to warm to room temperature over 30 minutes. The mixture was then heated on a water bath at 60°C for approximately 3 hours, until the evolution of gas ceased and the violet colouration of the acyl azide had disappeared. After cooling, the pale brown liquid was poured onto crushed ice and made alkaline with NH_4OH. The resultant yellow precipitate was filtered off and dried. Yield 4.2 g, 100%. Melting point 105-107°C.

Spectral data was in agreement with product isolated from Method A.

EXAMPLE 3. 2,4-Dichloroquinoline



C_9H_7N
Mol. Wt: 93.1

$C_9H_5Cl_2N$
Mol. Wt: 198.1

Aniline (6.7 g, 72 mmol) and malonic acid (11.7 g, 112 mmol) were heated under reflux in phosphorus oxychloride (60 ml), with stirring, for 5 hours. The mixture was cooled, poured into crushed ice with vigorous stirring and then made alkaline with 5M sodium hydroxide. Filtration gave the crude product as a brown solid. A four hour continuous (Soxhlet) extraction with hexane followed by evaporation of solvent under reduced pressure yielded a pale yellow powder. Tlc (95:5 hexane/ethyl acetate) gave two spots; R_f=0.51 and R_f=0.05. Column chromatography with 95:5 hexane:EtOAc as eluent yielded the pure product (R_f=0.51) as off-white needles, yield 6.8 g, 48%, m.p. 66-67°C.

Found M^+: 196.9792. $C_9H_5Cl_2N$ requires 196.9799.

δ_H: 8.18 (1H, dd, *J* 8.4, 1.3, H5), 8.03 (1H, dd, *J* 8.5, 1.0, H8), 7.79 (1H, ddd, *J* 8.5, 7.0, 1.3, H7), 7.65, (1H, ddd, *J* 8.4, 7.0, 1.0, H6), 7.50 (1H, s, H3).

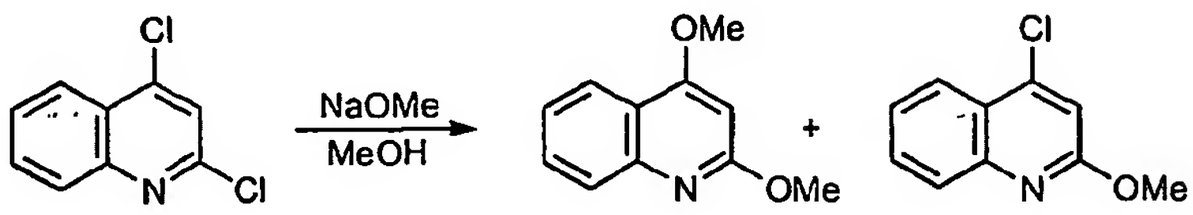
δ_C: 149.8 (C2), 148.1 (C8a), 144.4 (C4), 131.5 (C7), 129.0 (C8), 127.9 (C6), 125.2 (C4a), 124.2 (C5), 121.9 (C3).

n_{max} /cm^{-1}: 1580 (s, C=N), 720 (m, C-Cl).

m/z: 201 (15%, $M^+ {}^{37}Cl_2$), 199 (72%, $M^+ {}^{37}Cl^{35}Cl$), 197 (100%, $M^+ {}^{35}Cl_2$), 162 (69%, M^+ - Cl).

EXAMPLE 4A. 2,4-Dimethoxyquinoline and

EXAMPLE 4B. 4-chloro-2-methoxyquinoline



$C_9H_5Cl_2N$
Mol. Wt.: 198.1

$C_{11}H_{11}NO_2$
Mol. Wt.: 189.2

$C_{10}H_8ClNO$
Mol. Wt.: 193.6

2,4-Dichloroquinoline (2.8 g, 14 mmol) was heated under reflux in methanolic sodium methoxide solution (from 2.0 g, 86 mmol Na in 50 ml MeOH) for 24 hours. The reaction mixture was cooled and poured into ice-cold water, and the resulting white precipitate was filtered off. Tlc (95:5 hexane:EtOAc) gave two spots, R_f 0.61 and 0.48. Column chromatography with 9:1 hexane:EtOAc yielded the two products 2,4-dimethoxyquinoline (R_f 0.48), 1.85 g, 70% and 4-chloro-2-methoxyquinoline (R_f 0.61), 0.32 g, 12%, both as white needles.

Data for 2,4-dimethoxyquinoline (EXAMPLE 4A)

Melting point 78-80°C.

Found M^+: 189.0797. $C_{11}H_{11}NO_2$ requires 189.0790.

δ_H: 8.04 (1H, dd, *J* 8.2, 1.5, H5), 7.78 (1H, dd, *J* 8.5, 1.2, H8), 7.60 (1H, ddd, *J* 8.5, 7.0, 1.5, H7), 7.33 (1H, ddd, *J* 8.2, 7.0, 1.2, H6), 6.21(1H, s, H3), 4.05 (3H, s, 2-OMe), 3.97 (3H, s, 4-OMe).

δ_C : 163.9 (C4), 163.84 (C2), 147.1 (C8a), 130.0 (C7), 126.9 (C8), 123.3 (C6), 121.8 (C5), 119.3 (C4a), 90.7 (C3), 55.7 (4-OMe), 53.4 (2-OMe).

N.O.E: Irradiation at d3.97 ppm gave enhancement of H3 (6.21 ppm).
Irradiation at d4.05 ppm gave weak enhancement of H3 (6.21 ppm).

n_{max} /cm^{-1}: 1640, 1580 (s, C=N, C=C)

m/z: 189 (100%, M^+), 188 (93%, M^+ - H).

Data for 4-chloro-2-methoxyquinoline (EXAMPLE 4B)

Melting point 70-72°C.

Found M^+: 193.0298. $C_{10}H_8{}^{35}ClNO$ requires 193.0294.

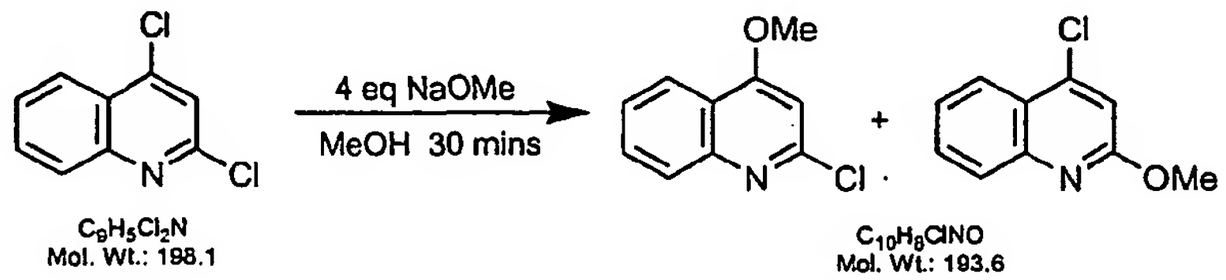
δ_H: 8.10 (1H, dd, *J* 8.2, 1.3, H5), 7.86 (1H, dd, *J* 8.0, 1.2, H8), 7.67 (1H, ddd, *J* 8.0, 7.0, 1.3, H7), 7.46 (1H, ddd, *J* 8.2, 7.0, 1.2, H6), 7.03 (1H, s, H3), 4.06 (3H, s, $-OCH_3$).

δ_C: 161.9 (C2), 147.0 (C8a), 143.7 (C4), 130.5 (C7), 127.6 (C8), 124.8 (C6), 124.1 (C5), 123.3 (C4a), 112.9 (C3), 53.8 (OCH_3).

n_{max} /cm^{-1}: 1610, 1580 (s, C=N and C=C).

m/z: 195 (33%, M^+ ^{37}Cl), 193 (100%, M^+ ^{35}Cl), 192 (67%, M^+ ^{35}Cl - H), 163 (33%, M^+ - CH_2O).

EXAMPLE 5. 2-Chloro-4-methoxyquinoline



$C_9H_5Cl_2N$
Mol. Wt.: 198.1

$C_{10}H_8ClNO$
Mol. Wt.: 193.6

2,4-Dichloroquinoline (1.5 g, 7.5 mmol) was heated under reflux in methanolic sodium methoxide (from 0.80 g, 34 mmol Na in 30 ml methanol) for 30 minutes. The mixture was cooled, poured into ice-cold water and then filtered to give a pale yellowish solid. Tlc (4:1 hexane: EtOAc) showed three spots; R_f 0.73 (4-chloro 2-methoxyquinoline), 0.55 (starting material), 0.36 (2-chloro 4-methoxyquinoline). Column chromatography (4:1 hexane: EtOAc) yielded 0.35 g, 25% of the desired product as white needles, plus 0.5 g, 36% of 4-chloro-2-methoxyquinoline and 0.3 g of starting material. Melting point 73-75°C.

Found M^+: 193.0298. $C_{10}H_8{}^{35}ClNO$ requires 193.0294.

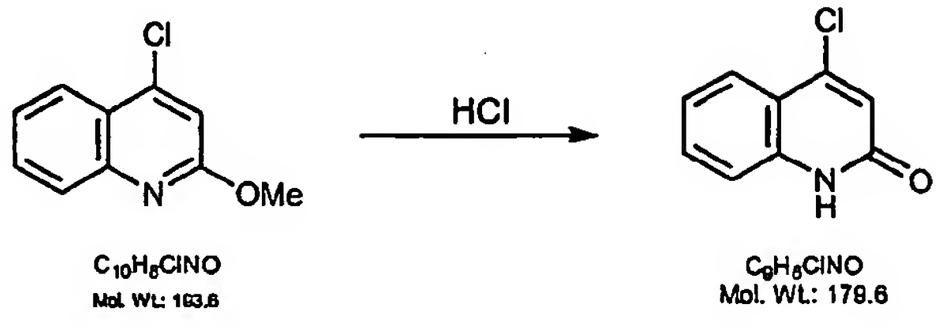
δ_H: 8.12 (1H, dd, *J* 8.5, 1.5, H5), 7.93 (1H, dd, *J* 8.2, 1.2, H8), 7.70 (1H, ddd, *J* 8.2, 6.9, 1.5, H7), 7.50 (1H, ddd, *J* 8.5, 6.9, 1.2, H6), 6.73 (1H, s, H3), 4.05 (3H, s, OCH_3).

δ_C: 163.8 (C4), 151.6 (C2), 148.1 (C8a), 130.9 (C7), 128.1 (C8), 126.1 (C6), 122.0 (C5), 120.4 (C4a), 101.2 (C3), 56.2 (MeO).

n_{max} /cm^{-1}: 1630, 1590, 1570 (s, C=N and C=C).

m/z: 195 (33%, M^+ ^{37}Cl), 193 (100%, M^+ ^{35}Cl), 179 (M^+ ^{35}Cl - CH_2), 158 (M^+ - Cl).

EXAMPLE 6. 4-Chloro-1*H*-quinolin-2-one



$C_{10}H_8ClNO$
Mol. Wt: 193.6

C_9H_6ClNO
Mol. Wt: 179.6

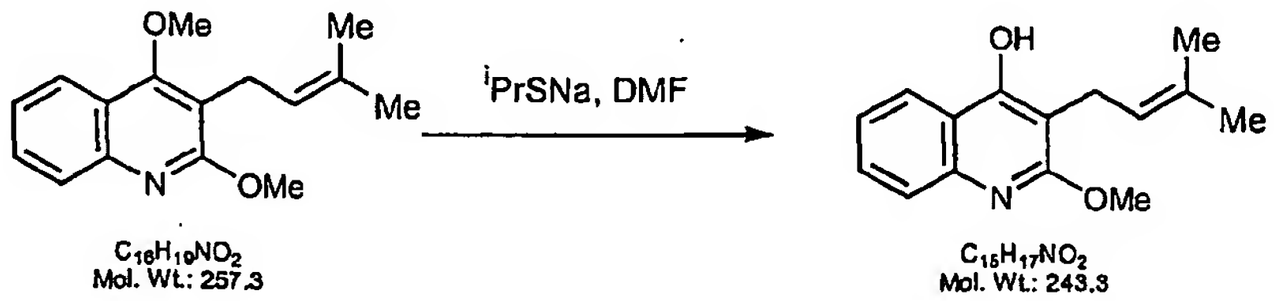
4-Chloro-2-methoxyquinoline (**EXAMPLE 4B**) (0.30 g, 1.6 mmol) was heated under reflux in 5M HCl (30 ml) for 45 minutes and then left to stand overnight. A small amount of white precipitate formed. After neutralisation with aqueous sodium carbonate the mixture was filtered to give the product (0.10 g, 36%) as a white powder which was insoluble even in polar solvents. Melting point 248-250°C.

Found M^+: 179.0143. C_9H_6ClNO requires 179.0138.

n_{max} /cm^{-1}: 3300 (m, N-H), 1670 (s, amide C=O).

m/z: 181 (33%, M^+, ^{37}Cl), 179 (100%, M^+, ^{35}Cl), 151 (75%, M^+ - CO), 89 (62%, $C_3H_2{}^{35}ClO^+$).

EXAMPLE 7. 4-Hydroxy-2-methoxy 3-(3-methylbut-2-enyl)quinoline



$C_{16}H_{19}NO_2$
Mol. Wt.: 257.3

$C_{15}H_{17}NO_2$
Mol. Wt.: 243.3

Sodium hydride (0.67 g of a 60% mineral oil dispersion, washed with hexane, 17 mmol) was suspended in dimethylformamide (10 ml). 2-Propanethiol (0.51 g, 6.7 mmol) was added and the mixture was stirred for 10 minutes. Then a solution

of 2,4-dimethoxy-3-(3-methylbut-2-enyl)quinoline (0.7 g, 2.7 mmol) in DMF (10 ml) was added, and the mixture heated under reflux for 4 hours. After cooling and neutralisation with 2M HCl the solution was extracted with ether (4 x 50 ml), the combined ether extracts were dried over $MgSO_4$, and the solvent removed *in vacuo* to give a brown oil. Tlc (4:1 hexane:EtOAc) revealed the presence of both starting material (R_f 0.57) and a product (R_f 0.30). Column chromatography (4:1 hexane:ethyl acetate) followed by recrystallisation (ethanol) yielded the pure product (0.25 g, 38%) as off-white needles. Melting point: 154-155°C.

Found M^+: 243.1246. $C_{15}H_{17}NO_2$ requires 243.1259.

δ_H: 7.98 (1H, dd, *J* 8.2, 1.3, H5), 7.75 (1H, dd, *J* 8.2, 1.2, H8), 7.56 (1H, ddd, *J* 8.3, 6.9, 1.3, H7), 7.32 (1H, ddd, *J* 8.2, 6.9, 1.2, H6), 5.38 (1H, tq, *J* 7.3, 1.2, C<u>H</u>=), 4.06 (3H, s, OCH_3), 3.51 (2H, d, *J* 7.3, $C\underline{H_2}CH$=), 1.86 (3H, s, CH=CC<u>H_3</u>) 1.81 (3H, d, *J* 1.2, CH=CC<u>H_3</u>). OH not observed in $CDCl_3$.

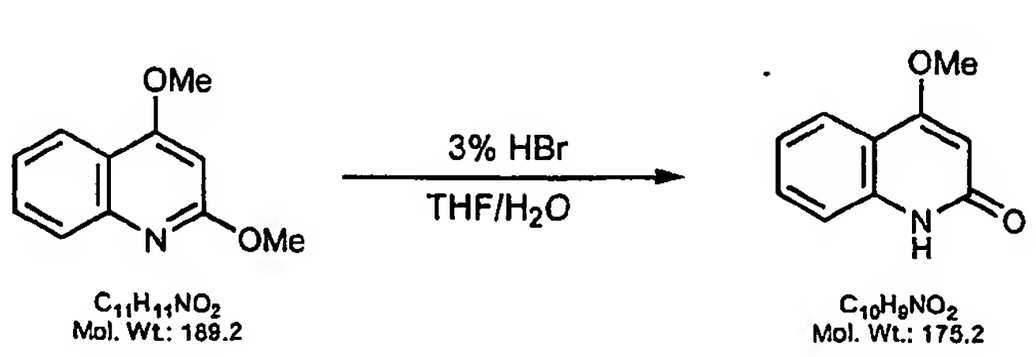
δ_C: 161.4 (C2), 145.0 (C8a), 137.0 (=<u>C</u>$(CH_3)_2$), 129.3, 126.5, 123.2, 121.6, 121.1 (C5,6,7,8 and =<u>C</u>H), 119.0 (C4a), 105.2 (C3), 53.9 (OMe), 25.9 (CH_3), 23.0 (CH_2), 18.0 (CH_3), no signal observed for C4.

NOESY (DMSO d_6): correlation between the OH proton at d11.5 ppm and the C5 proton at δ7.98 ppm.

n_{max} /cm^{-1}: 3200-3000 (br, O-H), 1627, 1580 (s, C=C, C=N)

m/z: 243 (26%, M^+), 228 (12%, M^+ - CH_3), 188 (5%, M^+ - $CH=C(CH_3)_2$), 83 (100%).

EXAMPLE 8. 4-Methoxy-1*H*-quinolin-2-one



$C_{11}H_{11}NO_2$
Mol. Wt: 189.2

$C_{10}H_9NO_2$
Mol. Wt.: 175.2

2,4-Dimethoxyquinoline (**EXAMPLE 4A**) (2.0 g, 11 mmol) was dissolved in 3% HBr in a 1:1 mixture of H_2O/THF (100 ml). The solution was heated under reflux

for 3 hours, then cooled and neutralised with aqueous $NaHCO_3$. The THF was removed under reduced pressure, precipitating a white solid, which was filtered and dried under suction. Tlc (4:1 hexane:EtOAc) showed the presence of starting material and a polar material (baseline). A 5 hour Soxhlet extraction with hexane separated these two compounds. The starting material was extracted into the reaction flask leaving the product, cream needles, in the thimble. Yield 1.0 g, 54%. Melting point 249-252°C.

Found M^+: 175.0629. $C_{10}H_9NO_2$ requires 175.0633.

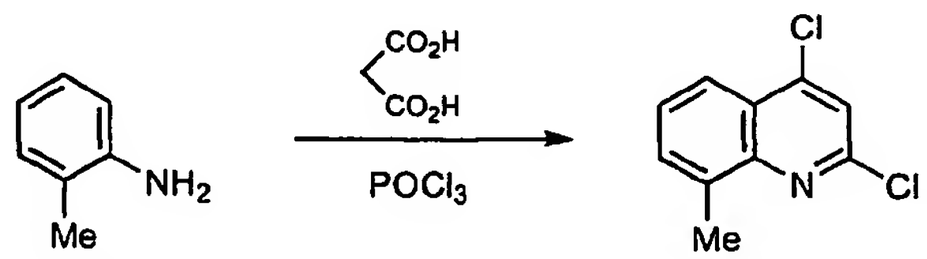
δ_H: 7.90 (1H, dd, *J* 8.1, 1.1, H5), 7.52 (1H, dd, *J* 8.1, 1.1, H7), 7.40 (1H, dd, *J* 8.1, 1.1, H8), 7.20 (1H, dd, *J* 8.1, 1.1, H6), 6.03 (1H, s, H3), 3.99 (3H, s, OMe).

δ_C: 166.3 (C2), 165.0 (C4), 138.4 (C8a), 131.2 (C7), 122.8 (C8), 122.2 (C6), 116.1 (C5), 115.6 (C4a), 96.0 (C3), 56.0 (OMe).

n_{max} /cm^{-1}: 3100 (w, N-H), 1674 (s, C=O), 1634, 1607 (s, C=C).

m/z: 175 (100%, M^+), 132 (63%, M^+ - CONH), 76 (28%, $C_6H_4^+$).

EXAMPLE 9. 2,4-Dichloro-8-methylquinoline



C_7H_9N
Mol. Wt: 107.2

$C_{10}H_7Cl_2N$
Mol. Wt: 212.1

o-Toluidine (5.0 g, 47 mmol), malonic acid (7.3 g, 70 mmol) and $POCl_3$ (40 ml) were heated under reflux for 5 hours. Aqueous workup was as for other dichloroquinolines to give the crude product as a brown powder. After continuous extraction of the crude product (hexane, 4h) the pure quinoline was obtained as a yellow powder. Yield 5.3 g, 53%. R_f (9:1 hexane:EtOAc) 0.70. Melting point 80-82°C.

Found M^+: 210.9956. $C_{10}H_7{}^{35}Cl_2N$ requires 210.9955.

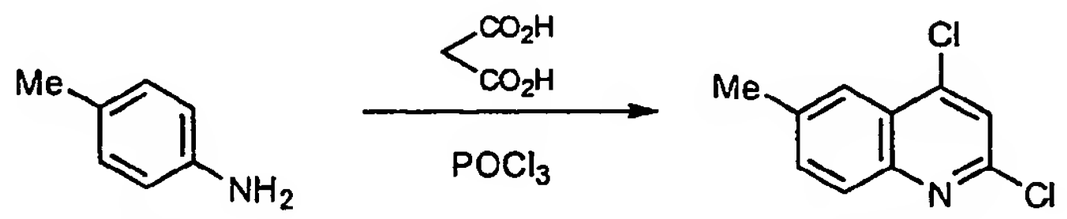
δ_H: 7.95 (1H, d, *J* 8.3, H5), 7.54 (1H, d, *J* 7.1, H7), 7.44 (1H dd, *J* 8.3, 7.1, H6), 7.40 (1H, s, H3), 2.68 (3H, s, 8-Me).

δ_C: 147.6 (C2), 146.3 (C8a), 143.3 (C4), 136.2 (C8), 130.6 (C7), 126.5 (C6), 124.2 (C4a), 121.0 (C5), 120.7 (C3), 17.1 (8-Me).

n_{max} /cm^{-1}: 1610, 1573 (s, C=C and C=N) 680 (w, C-Cl).

m/z: 215 (13%, M^+ $^{37}Cl_2$), 213 (79%, M^+ $^{37}Cl^{35}Cl$), 211 (100%, M^+ $^{35}Cl_2$), 176 (22%, M^+ - Cl), 148 (14%), 140 (24%, M^+ - 2Cl).

EXAMPLE 10. 2,4-Dichloro-6-methylquinoline



C_7H_9N
Mol. Wt.: 107.2

$C_{10}H_7Cl_2N$
Mol. Wt.: 212.1

Malonic acid (7.3 g, 70 mmol) and *p*-toluidine (5.0 g, 47 mmol) were heated under reflux in phosphorus oxychloride (40 ml) for 5 hours. After cooling, the reaction mixture was poured onto crushed ice and neutralised (NaOH). The crude brown precipitate was filtered off and then and purified by Soxhlet extraction (hexane), to give the title compound as a pale yellow powder. Yield 5.1 g, 51%. Melting point 91-93°C.

Found M^+: 210.9955. $C_{10}H_7{}^{35}Cl_2N$ requires 210.9955.

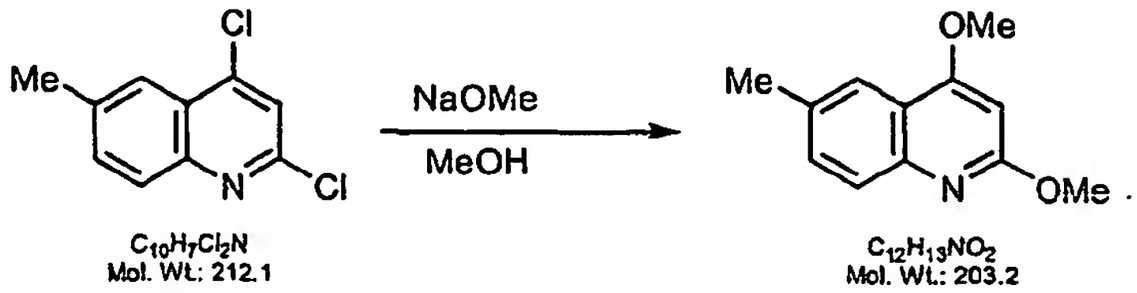
δ_H: 7.91-7.88 (2H, m, H5 and H8), 7.60 (1H, dd, *J* 8.6, 1.9, H7), 7.44 (1H, s, H3), 2.56 (3H, s, 6-Me).

δ_C: 148.8, 146.7 (C2, C4), 143.6 (C8a), 138.3 (C6), 133.7 (CH), 128.7 (CH), 125.1 (C4a), 123.1 (CH), 121.9 (CH), 21.9 (6-Me).

n_{max} /cm^{-1}: 1573, 1558 (m, C=C, C=N).

m/z: 215 (14%, M^+, $^{37}Cl_2$), 213 (34%, M^+, $^{37}Cl^{35}Cl$), 211 (100%, M^+, $^{35}Cl_2$), 176 (28%, M^+ - Cl), 140 (29%).

EXAMPLE 11. 2,4-Dimethoxy-6-methylquinoline



$C_{10}H_7Cl_2N$
Mol. Wt: 212.1

$C_{12}H_{13}NO_2$
Mol. Wt.: 203.2

2,4-Dichloro-6-methylquinoline (**EXAMPLE 10**) (2.0 g, 9.4 mmol) was heated under reflux in methanolic sodium methoxide (2.0 g Na in 100 ml MeOH), for 40 hours, then cooled, poured into cold water and filtered to give the product as off-white needles. Yield 1.6 g, 84%. Melting point 53-55°C.

Found M^+: 203.0947. $C_{12}H_{13}NO_2$ requires 203.0946.

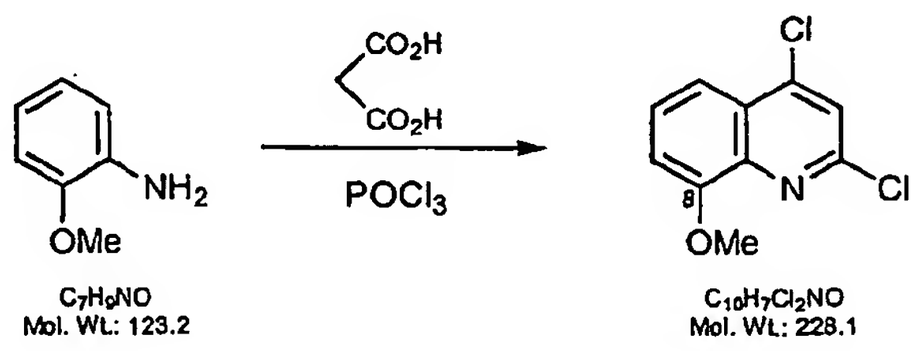
δ_H: 7.81 (1H, d, *J* 1.9, H5), 7.67 (1H, d, *J* 8.5, H8), 7.41 (1H, dd, *J* 8.5, 1.9, H7), 6.18 (1H, s, H3), 4.03 (3H, s, OMe), 3.95 (3H, s, OMe), 2.46 (3H, s, Me).

δ_C: 163.9, 163.7 (C2, C4), 145.7 (C8a), 133.3 (C6), 132.2, 127.0, 121.4, (C5, C7, C8), 119.4 (C4a), 91.0 (C3), 56.0 (OMe), 53.7 (OMe), 21.8 (Me).

n_{max} /cm^{-1}: 1631, 1609, 1581 (s, C=C and C=N).

m/z: 203 (93%, M^+), 202 (100%, M^+ - H), 174 (22%, M^+ - OMe), 173 (36%, M^+ - OMe, H).

EXAMPLE 12. 2,4-Dichloro-8-methoxyquinoline



C_7H_9NO
Mol. Wt.: 123.2

$C_{10}H_7Cl_2NO$
Mol. Wt.: 228.1

o-Anisidine (3.0 g, 24 mmol) and malonic acid (3.7 g, 36 mmol) were heated under reflux in phosphorus oxychloride (35 ml) for 5 hours, followed by aqueous alkaline workup and filtration to give a brown solid. Soxhlet extraction of the crude

product with hexane gave the title compound as an off-white powder. Yield 1.45 g, 26%. Melting point 132-135°C.

Found M^+: 226.9909. $C_{10}H_7{}^{35}Cl_2NO$ requires 226.9905.

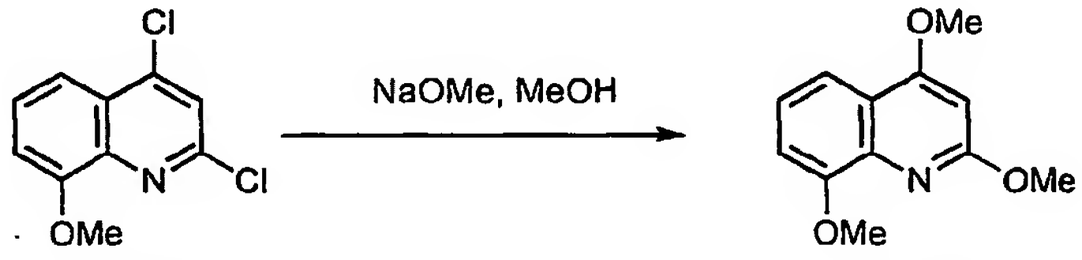
δ_H: 7.74 (1H, dd, *J* 8.5, 1.1, H5), 7.55 (1H, dd, *J* 8.5, 7.0, H6), 7.53 (1H, s, H3), 7.14 (1H, dd, *J* 7.0, 1.1, H7), 4.07 (3H, s, OMe).

δ_C: 154.8, 148.9, 144.3, 139.9 (C2, C4, C8, C8a), 128.1, 126.3 (C4a), 122.7, 115.7, 109.8, 56.3 (OMe).

n_{max} /cm^{-1}: 1616, 1576, 1559 (s, C=C, C=N).

m/z: 231 (19%, $M^+ {}^{37}Cl_2$), 230 (16%, $M^+ {}^{37}Cl_2$ - H), 229 (68%, $M^+ {}^{37}Cl^{35}Cl$), 228 (84%, $M^+ {}^{37}Cl^{35}Cl$ - H), 227 (92%, $M^+ {}^{35}Cl_2$), 226 (100%, $M^+ {}^{35}Cl_2$ - H), 198 (94%), 162 (59%).

EXAMPLE 13. 2,4,8 -Trimethoxyquinoline



$C_{10}H_7Cl_2NO$
Mol. Wt.: 228.1

$C_{12}H_{13}NO_3$
Mol. Wt.: 219.2

2,4-Dichloro-8-methoxyquinoline (**EXAMPLE 12**) (1.0 g, 4.4 mmol) was heated under reflux in methanolic sodium methoxide (1.0 g Na in 50 ml MeOH) for 48 hours. After cooling, the mixture was poured into cold water and the product, white fluffy needles, obtained by filtration. Yield 0.67 g, 70%. Melting point 149-150°C.

Found M^+: 219.0899. $C_{12}H_{13}NO_3$ requires 219.0895.

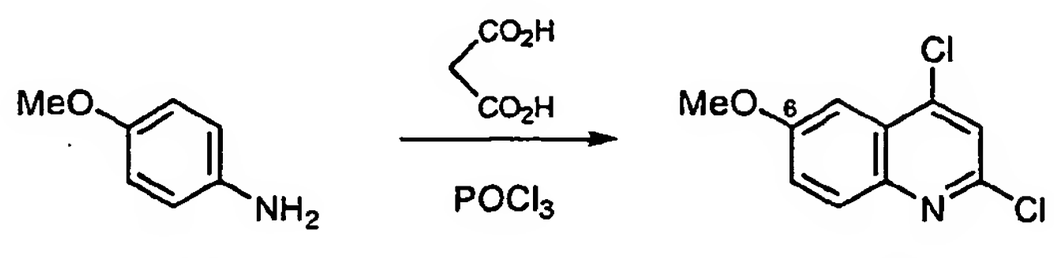
δ_H: 7.65 (1H, dd, *J* 8.2, 0.8, H5), 7.26 (1H, dd, *J* 8.2, 7.8, H6), 7.03 (1H, dd, *J* 7.8, 0.8, H7), 6.26 (1H, s, H3), 4.12 (3H, s, 8-OMe), 4.04 (3H, s, OMe), 3.98 (3H, s, OMe).

δ_C: 164.4, 163.9 (C2, C4), 154.3 (C8), 138.7 (C8a), 123.6 (C6), 120.9 (C4a), 114.2, 109.9 (C5, C7), 91.5 (C3), 56.7, 56.1 53.8 (3 x OMe).

n_{max}/cm^{-1}: 1621, 1603, 1580 (s, C=C, C=N), 1082, 1044 (s, C-O-C).

m/z: 219 (10%, M^+), 218 (90%, M^+ - H), 204 (36%, M^+ - Me), 189 (44%, M^+ - 2Me).

EXAMPLE 14. 2,4-Dichloro-6-methoxyquinoline



C_7H_9NO Mol. Wt.: 123.2

$C_{10}H_7Cl_2NO$ Mol. Wt.: 228.1

p-Anisidine (5.0 g, 41 mmol), malonic acid (6.5 g, 63 mmol), and phosphorus oxychloride (40 ml) were heated under reflux for 4 hours. Standard workup gave the crude product as a black solid, from which Soxhlet extraction with hexane yielded 5.1 g, 55% of the title compound as white needles. Melting point: 168-170°C.

Found M^+: 226.9917. $C_{10}H_7{}^{35}Cl_2NO$ requires 226.9905.

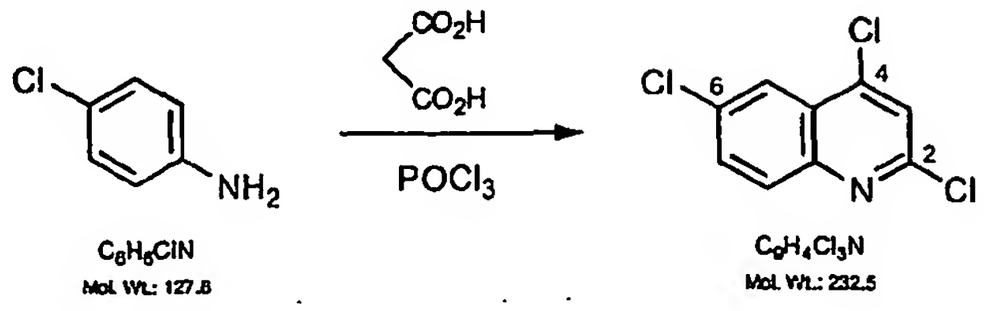
δ_H: 7.84 (1H, d, *J* 9.1, H8), 7.40 (1H, s, H3), 7.35 (1H, dd, *J* 9.1, 2.7, H7), 7.31 (1H, d, *J* 2.7, H5), 3.89 (3H, s, OMe).

δ_C: 158.9, 147.0, 144.1, 142.7 (C2, C4, C6, C8a), 130.5 (CH), 126.3 (C4a), 124.1 (CH), 122.0 (CH), 102.0 (C3), 55.8 (OMe).

n_{max}/cm^{-1}: 1622, 1563 (s, C=C and C=N).

m/z: 229 (36%, M^+ $^{35}Cl^{37}Cl$), 227 (49%, M^+ $^{35}Cl_2$), 143 (41%), 113 (66%).

EXAMPLE 15. 2,4,6-Trichloroquinoline



C8H6ClN
Mol. Wt.: 127.6

C9H4Cl3N
Mol. Wt.: 232.5

4-Chloroaniline (7.0 g, 54 mmol), malonic acid (8.5 g, 82 mmol) and phosphorus oxychloride (50 ml) were heated under reflux for 6 hours. Standard aqueous workup gave the crude product as a red-brown solid. Soxhlet extraction with hexane gave the pure product as a yellow powder. Yield 3.0 g, 24%. Melting point 116-118°C.

Found M^+: 230.9417. $C_9H_4{}^{35}Cl_3N$ requires 230.9409.

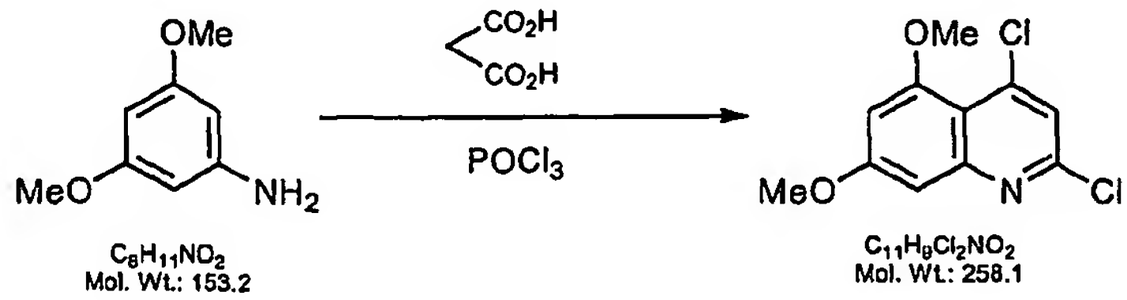
δ_H: 8.17 (1H, d, *J* 2.3, H5), 7.97 (1H, d, *J* 8.9, H8), 7.73 (1H, dd, *J* 8.9, 2.3, H7), 7.54 (1H, s, H3).

δ_C: 150.2 (C2), 146.5 (C4), 143.3 (C8a), 134.2 (C6), 132.5 (C8), 130.6 (C7), 125.9 (C4a), 123.3 (C5), 122.8 (C3).

n_{max} /cm^{-1}: 1571 (s, C=C or C=N).

m/z: 235 (36%, $M^+ {}^{37}Cl_2{}^{35}Cl$), 233 (97%, $M^+ {}^{37}Cl{}^{35}Cl_2$), 231 (100%, $M^+ {}^{35}Cl_3$), 196 (54%, M^+ - Cl), 163 (13%, $C_9H_4{}^{37}ClN^+$), 161 (38%, $C_9H_4{}^{35}ClN^+$).

EXAMPLE 16. 2,4-Dichloro-5,7-dimethoxyquinoline



C8H11NO2
Mol. Wt.: 153.2

C11H9Cl2NO2
Mol. Wt.: 258.1

3,5-Dimethoxyaniline (3.0 g, 20 mmol) and malonic acid (3.1 g, 30 mmol) were heated under reflux in phosphorus oxychloride (30 ml) for 5 hours. The mixture was poured into crushed ice and made alkaline with 5M NaOH, then filtered to

give the crude product as a black solid. Soxhlet extraction with hexane furnished the product as pale yellow needles. Yield 0.9 g, 18%. Melting point: 160-162°C dec.

Found M^+: 257.0007. $C_{11}H_9{}^{35}Cl_2NO_2$ requires 257.0010.

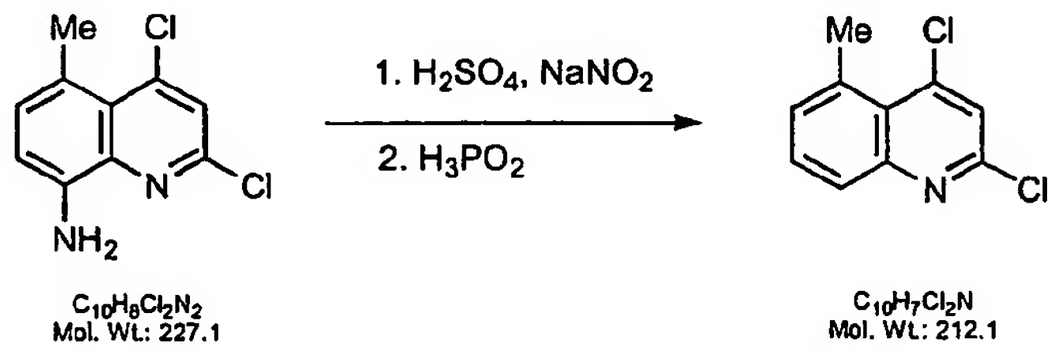
δ_H: 7.22 (1H, s, H3), 6.94 (1H, d, *J* 2.3, H8), 6.53 (1H, d, *J* 2.3, H6), 3.92 (3H, s, OMe), 3.91 (3H, s, OMe).

δ_C: 162.5, 157.5, 152.4, 150.7 (C2, C4, C5, C7), 143.3 (C8a), 121.4 (C3), 113.3 (C4a), 100.7, 100.5, (C5, C7) 56.3 (OMe), 56.1 (OMe).

n_{max} / cm^{-1}: 1617, 1577, 1558 (s, C=C, C=N).

m/z: 261 (11%, $M^+ {}^{37}Cl_2$), 259 (54%, $M^+ {}^{37}Cl{}^{35}Cl$), 257 (100%, $M^+ {}^{35}Cl_2$), 212 (8%), 149 (9%).

EXAMPLE 17. 2,4-Dichloro-5-methylquinoline



$C_{10}H_8Cl_2N_2$
Mol. Wt: 227.1

$C_{10}H_7Cl_2N$
Mol. Wt: 212.1

8-Amino-2,4-dichloro-5-methylquinoline (**EXAMPLE 45**) (0.10 g, 0.44 mmol) was added to 49% sulfuric acid (6.0 ml) at 0°C, with stirring. Powdered sodium nitrite (35 mg, 0.50 mmol) was added and the mixture maintained at 0°C for 15 minutes before pouring into 30% hypophosphorous acid (20 ml) at 0°C. The reaction mixture was then slowly warmed to 40°C, until evolution of nitrogen ceased. The mixture was poured into crushed ice, neutralised with 2M NaOH, and extracted with diethyl ether (3 x 50 ml). The combined ether layers were dried over $MgSO_4$, and the solvent evaporated under reduced pressure to give a pale orange solid, R_f (9:1 hexane:EtOAc) 0.52. Yield 75 mg, 80%. Melting point: 126-129°C.

Found M^+: 210.9998. $C_{10}H_7{}^{35}Cl_2N$ requires 211.0081.

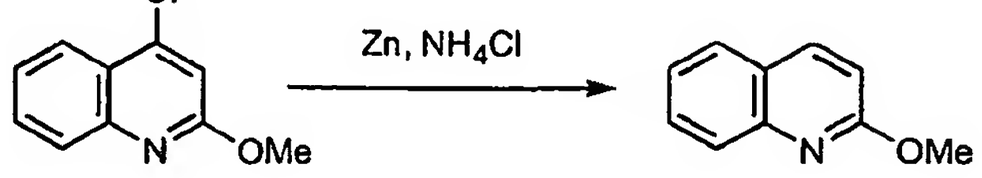
δ_H: 7.89 (1H, d, *J* 8.4, H8), 7.60 (1H, dd, *J* 8.4, 7.2, H7), 7.46 (1H, s, H3), 7.37 (1H, d, *J* 7.2, H6), 3.01 (3H, s, 5-Me).

δ_C: 150.2, 149.0, 144.5, 135.7, 131.2, 130.7, 128.2, 124.6, 123.7, 25.2 (5-Me).

n_{max} /cm^{-1}: 1570, 1557 (s, C=C, C≡N).

m/z: 215 (11%, M^+ $^{37}Cl_2$), 213 (64%, M^+ $^{37}Cl^{35}Cl$), 211 (100%, M^+ $^{35}Cl_2$), 176 (34%, M^+ - Cl), 140 (25%).

EXAMPLE 18. 2-Methoxyquinoline



$C_{10}H_8ClNO$
Mol. Wt.: 193.6

$C_{10}H_9NO$
Mol. Wt.: 159.2

4-Chloro-2-methoxyquinoline (**EXAMPLE 4B**) (0.40 g, 2.1 mmol), zinc dust (0.70 g, 11 mmol) and ammonium chloride (0.70 g, 13 mmol) were heated under reflux in 50% aqueous ethanol (30 ml) for 2 hours. After cooling, the mixture was extracted with diethyl ether (3 x 30 ml), the combined organic extracts were dried ($MgSO_4$), and the solvent removed *in vacuo* to give a brown oil which was purified by column chromatography (9:1 hexane:EtOAc). The title compound (R_f 0.35) was obtained as a sweet-smelling colourless oil. Yield 0.25 g, 75%.

Found M^+: 159.0674. $C_{10}H_9NO$ requires 159.0684.

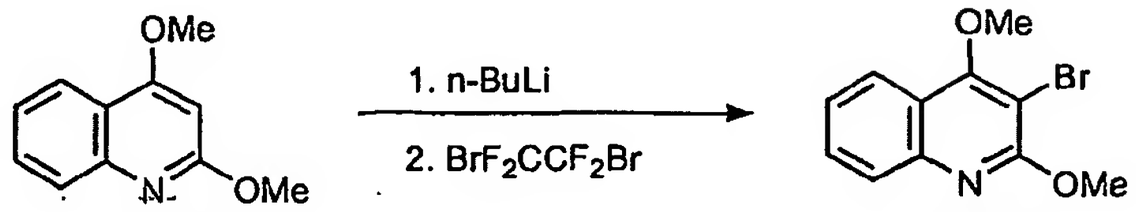
δ_H: 7.95 (1H, d, *J* 8.8, H4), 7.85 (1H, d, *J* 8.4, H8), 7.70 (1H, d, *J* 8.0, H5), 7.61 (1H, dd, *J* 8.4, 7.0, H7), 7.36 (1H, dd, *J* 8.0, 7.0, H6), 6.89 (1H, d, *J* 8.8, H3), 4.07 (3H, s, OMe).

δ_C: 162.8 (C2), 147.0 (C3), 139.1 (C4), 129.9, 127.9, 127.6, 125.5 (C4a), 124.4, 113.5 (C3), 53.8 (OMe).

n_{max}/cm^{-1}: 3060, 3010, 2944 (m, C-H), 1619, 1571 (s, C=C, C=N), 1026 (s, C-O).

m/z: 159 (100%, M^+), 158 (98%, M^+ - H), 129 (80%, $C_9H_7N^+$).

EXAMPLE 19. 3-Bromo 2,4-dimethoxyquinoline



$C_{11}H_{11}NO_2$
Mol Wt: 189.2

$C_{11}H_{10}BrNO_2$
Mol. Wt: 268.1

2,4-Dimethoxyquinoline (**EXAMPLE 4A**) (1.5 g, 7.9 mmol) was dissolved in dry THF (25 ml) and cooled to 0°C under argon. Then *n*-butyllithium (4.8 ml of a 2.5M solution in hexanes, 12 mmol) was added dropwise and the mixture was stirred at 0°C for 45 minutes. 1,2-Dibromo-tetrafluoroethane (3.3 g, 12.6 mmol) in THF (10 ml) was added slowly over 5 minutes. Stirring was continued at 0°C for 30 minutes and then with warming to room temperature for 1 hour. The colour changed from purple to black/brown. The mixture was poured into water and extracted with ether (4 x 100 ml). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a black sticky residue. Tlc (9:1 hexane:EtOAc) showed 2 spots; R_f 0.45 and baseline (highly coloured). Column chromatography (9:1 hexane:EtOAc) furnished the pure product (R_f 0.45) as off-white plates. Yield 0.9 g, 43%. Melting point: 67-69°C.

Found M^+: 266.9895. $C_{11}H_{10}{}^{79}BrNO_2$ requires 266.9894.

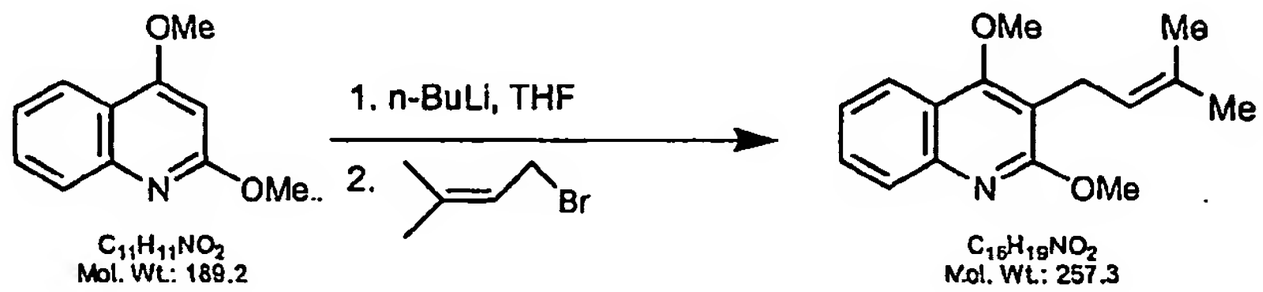
δ_H: 7.97 (1H, dd, *J* 8.2, 1.1, H5), 7.84 (1H, dd, *J* 8.5, 1.1, H8), 7.64 (1H, ddd, *J* 8.5, 7.0, 1.1, H7), 7.41 (1H, ddd *J* 8.2, 7.0, 1.1, H6), 4.14 (3H, s, OMe), 4.08 (3H, s, OMe).

δ_C: 162.4 (C2), 159.0 (C4), 145.9 (C8a), 130.2, 127.3, (C7, C8), 124.5, 122.0, (C5, C6), 100.4 (C4a), 61.6 (MeO), 54.8 (MeO). No signal observed for C3.

n_{max} /cm^{-1}: 1580, 1568 (s, C=C, C=N).

m/z: 267 (93%, M^+ ^{79}Br), 266 (95%, M^+ - H), 239 (62%, M^+ - OMe), 237 (56%, M^+ - OMe) (N.B. M^+, ^{81}Br lost due to coincidence with PFK internal reference).

EXAMPLE 20. 2,4 -Dimethoxy-3-(3methylbut-2-enyl)quinoline



$C_{11}H_{11}NO_2$
Mol. Wt: 189.2

$C_{16}H_{19}NO_2$
Mol. Wt: 257.3

2,4-Dimethoxyquinoline (**EXAMPLE 4A**) (2.0 g, 11 mmol) in dry THF (10 ml) was cooled to 0°C under argon and *n*-butyllithium (6.2 ml of a 2.5M solution in hexane) was added dropwise, with stirring. The mixture was stirred at 0°C under argon for 30 minutes, then 1-bromo-3-methylbut-2-ene (2.8 g, 19 mmol) was added dropwise over 5 minutes. The mixture was stirred at 0°C for 30 minutes and then allowed to warm to room temperature with stirring for a further hour. The reaction mixture was poured into water and extracted with ether (4 x 30 ml) to give the crude product as a yellow/brown oil. Column chromatography (4:1 hexane:EtOAc) yielded the pure product (R_f 0.57) as a yellow-brown oil. Yield 2.4 g, 88%.

Found M^+: 257.1417. $C_{16}H_{19}NO_2$ requires 257.1416.

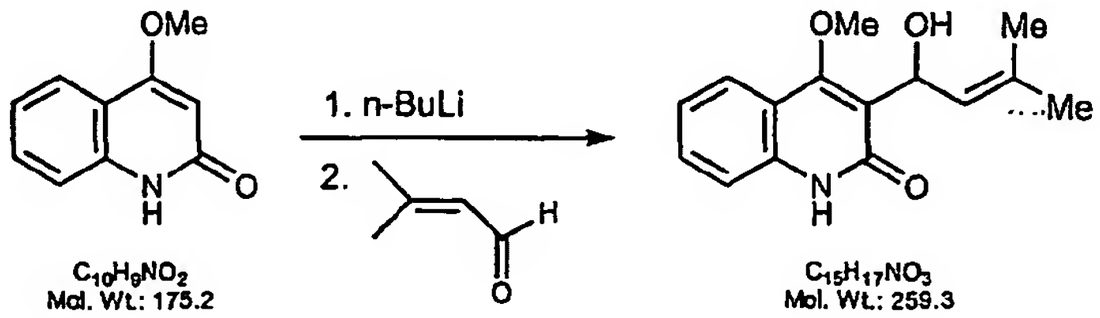
δ_H: 7.92 (1H, ddd, *J* 8.2, 1.5, 0.5, H5), 7.82 (1H, ddd, *J* 8.5, 1.2, 0.5, H8), 7.56 (1H, ddd, *J* 8.5, 6.9, 1.5, H7), 7.35 (1H, ddd, *J* 8.2, 6.9, 1.2, H6), 5.22 (1H, br t, *J* 6.9, C=C<u>H</u>), 4.08 (3H, s, 2-OMe), 3.95 (3H, s, 4-OMe), 3.45 (2H, d, *J* 6.9, C<u>H</u>$_2$), 1.81 (3H, d, *J* 0.7, =CC<u>H</u>$_3$), 1.69 (3H, d, *J* 1.2, =CC<u>H</u>$_3$).

δ_C: 162.5 (C4), 161.6 (C2), 146.1 (C8a), 132.3 (=<u>C</u>Me$_2$), 128.9, 127.3, (C7, C8) 123.6, 121.9, 121.8, (C5, C6 and =CH), 121.2 (C3), 116.9 (C4a), 62.3 (OMe), 53.8 (OMe), 25.8 (CH_3), 23.3 (CH_2), 18.0 (CH_3).

n_{max} /cm^{-1}: 3070 (s, C-H), 1620, 1605, 1575 (s, C=C and C=N).

m/z : 257 (100%, M^+), 242 (82%, M^+- Me), 202 (52%, M^+ - Me_2C=CH).

EXAMPLE 21. 3-(1-Hydroxy-3-methyl-but-2-enyl)-4-methoxy-1*H*-quinolin-2-one



$C_{10}H_9NO_2$
Mol. Wt: 175.2

$C_{15}H_{17}NO_3$
Mol. Wt: 259.3

4-Methoxyquinolin-2-one (0.80 g, 4.6 mmol) in THF (20 ml) was cooled to -78°C, and *n*-butyllithium (9.2 mmol) was added slowly, with stirring. The mixture was stirred at -78°C for 15 minutes, then allowed to warm to room temperature for 15 minutes, before cooling to -78°C once more. 3-Methylbut-2-enal (0.77 g, 9.2 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred for 15 minutes before being allowed to warm to room temperature and stirred for a further hour. The yellow solution was poured into water, and extracted with ether (3 x 50 ml). The combined organic layers were dried over $MgSO_4$, and the solvent removed *in vacuo* to give a white powder, R_f (1:1 hexane:ethyl acetate) 0.30. Yield 0.18 g, 15%. Melting point 128-130°C.

Found M^+: 259.1179. $C_{15}H_{17}NO_3$ requires 259.1208.

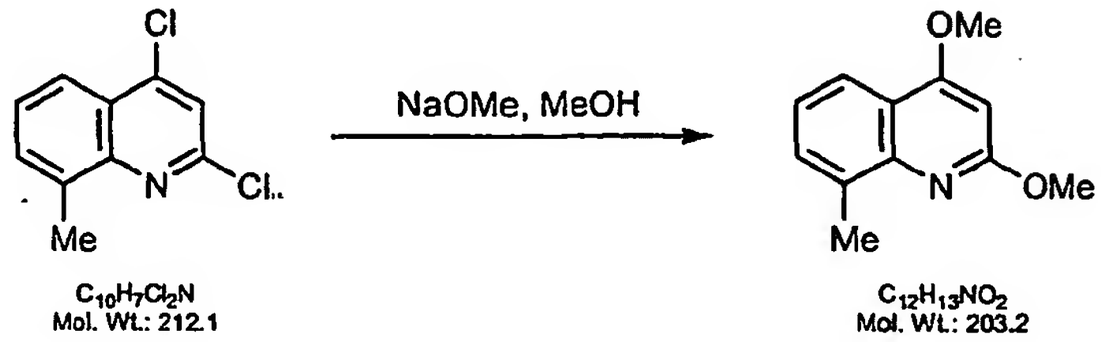
δ_H: 12.73 (1H, s, NH/OH), 7.73 (1H, d, *J* 8.1, H5), 7.47 (1H, m, H7), 7.38 (1H, d, *J* 8.0, H8), 7.20 (1H, m, H6), 5.77 (1H, d, *J* 9.2, CH-O<u>H</u>), 5.69 (1H, dd, *J* 10.5, 9.2, C<u>H</u>OH), 5.30 (1H, d, *J* 10.5, =C<u>H</u>), 3.92 (3H, s, OMe), 1.81 (3H, s, Me), 1.66 (3H, s, Me).

δ_C: 166.2, 161.5 (C2, C4), 137.7, 135.5 (C8a, Me_2<u>C</u>=), 130.9, (CH) 125.9 (CH), 123.4 (CH), 123.1 (CH), 117.1 (C4a), 116.4 (CH), 64.9 (OMe), 62.5 (OMe), 26.0 (Me), 18.3 (Me). No signal observed for C3.

n_{max} / cm^{-1}: 3462 (m, OH), 1644 (s, C=O), 1608 (s, C=C).

m/z (CI): 259 15%, M^+), 242 (43%, M^+ - OH), 241 (17%, M^+ - H_2O), 188 (49%), 175 (100%, M^+ - Me_2C=CHCHOH).

EXAMPLE 22. 2,4-Dimethoxy-8-methylquinoline



$C_{10}H_7Cl_2N$
Mol. Wt.: 212.1

$C_{12}H_{13}NO_2$
Mol. Wt.: 203.2

2,4-Dichloro-8-methylquinoline (**EXAMPLE 9**) (2.0 g, 9.4 mmol) was heated under reflux in methanolic sodium methoxide (from 4.0 g Na in 100 ml MeOH) for 40 hours, then cooled and poured into ice-cold water. The product was obtained by filtration as off-white needles. Yield 1.7 g, 89%. Melting point: 52-54°C.

Found M^+: 203.0911. $C_{12}H_{13}NO_2$ requires 203.0946.

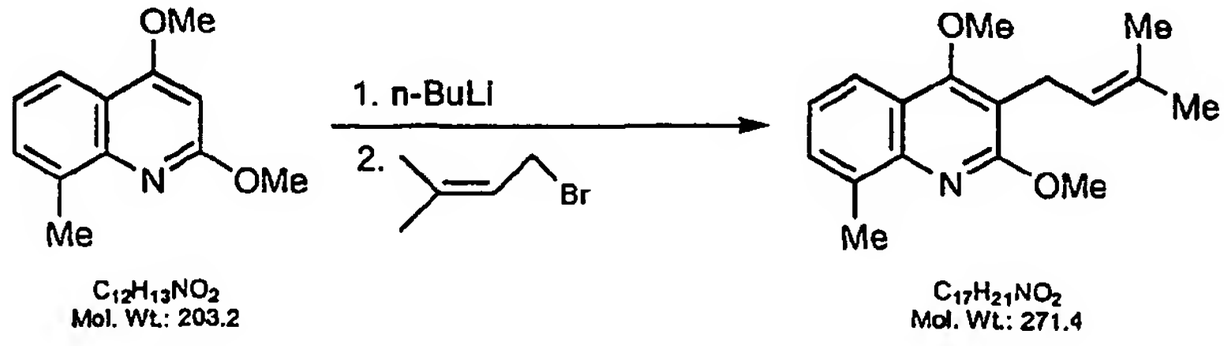
δ_H: 7.89 (1H, d, *J* 8.2, H5), 7.45 (1H, d, *J* 7.0, H7), 7.21 (1H, dd, *J* 8.2, 7.0, H6), 6.20 (1H, s, H3), 4.05 (3H, s, OMe), 3.94 (3H, s, OMe), 2.67 (3H, s, 8-Me)

δ_C: 164.1 (C4), 162.5 (C2), 145.8 (C8a), 134.9 (C8), 130.1 (C7), 122.7 (C6), 119.4 (C5), 118.9 (C4a), 90.1 (C3), 55.6 (OMe), 53.1 (OMe), 18.0 (8-Me).

ν_{max} /cm-1: 1620, 1580 (s, C=C, C=N).

m/z: 203 (51%, M^+), 202 (32%, M^+ - H), 193 (17%), 188 (22%, M^+ - Me), 173 (12%) 162 (16%).

EXAMPLE 23. 2,4-Dimethoxy-3-(3-methyl but-2-enyl)-8-methylquinoline



$C_{12}H_{13}NO_2$
Mol. Wt.: 203.2

$C_{17}H_{21}NO_2$
Mol. Wt.: 271.4

2,4-Dimethoxy-8-methylquinoline (**EXAMPLE 22**) (1.0 g, 4.9 mmol) was dissolved in dry THF (10 ml) and cooled to 0°C under argon. *n*-Butyllithium (3.0 ml of a 2.5M solution in hexane, 7.5 mmol) was added slowly with stirring, and the mixture

was stirred for 30 minutes at 0°C. 1-Bromo-3-methylbut-2-ene (1.3 g, 8.7 mmol) in THF (8 ml) was then added dropwise over 5 minutes. Stirring was continued for 30 minutes at 0°C and then the mixture was warmed to room temperature over 45 minutes. The resultant yellow-brown solution was poured into cold water and extracted with ether (3 x 50 ml). The combined ether extracts were dried over $MgSO_4$. Removal of solvent *in vacuo* yielded the crude product, a brown oil. Column chromatography (9:1 hexane:EtOAc) furnished the pure quinoline as a yellow-brown oil. Yield 1.1 g, 82%. R_f (9:1 hexane:EtOAc) 0.68.

Found M^+: 271.1562 . $C_{17}H_{21}NO_2$ requires 271.1572.

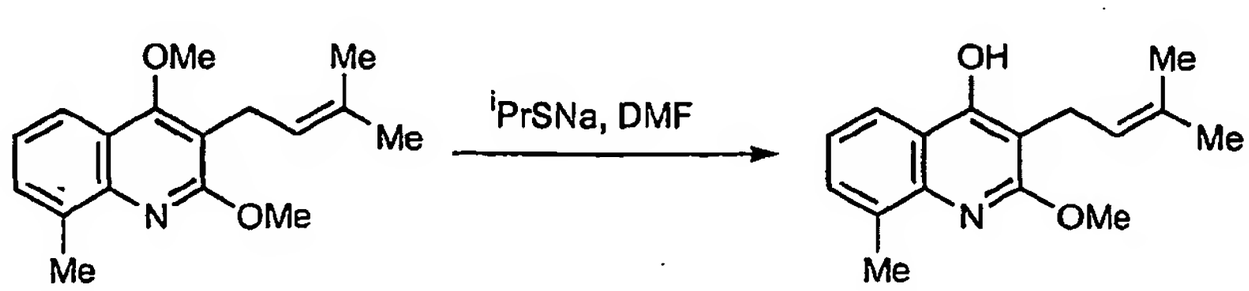
δ_H: 7.77 (1H, d, *J* 8.0, H5), 7.41 (1H, d, *J* 7.2, H7), 7.24 (1H, dd, *J* 7.2, 8.0, H6), 5.23 (1H, br t, *J* 7.0, =CH), 4.08 (3H, s, MeO), 3.92 (3H, s, MeO), 3.45 (2H, d, *J* 7.0, CH_2), 2.68 (3H, s, 8-Me), 1.81 (3H, s, $=CC\underline{H}_3$), 1.68 (3H, d, *J* 0.8, $=CC\underline{H}_3$)

δ_C: 161.8, 161.3 (C2 and C4), 144.8 (C9), 135.4, 132.1 (C8 and $=C(CH_3)_2$), 129.1, 123.2, 122.0, 120.9 (C5,6,7 and =CH), 119.6 (C10), 116.3 (C3), 62.2 (MeO), 53.5 (MeO), 25.8 (CH_3), 23.2 (CH_2), 17.9, 17.8(8-Me, CH_3).

n_{max} /cm^{-1}: 1619, 1583 (m, C=C, C=N).

m/z: 271 (100%, M^+), 256 (78%, M^+ - Me), 224 (34%), 202 (33%, $C_{12}H_{12}NO_2^+$).

EXAMPLE 24. 4-Hydroxy-2-methoxy-8-methyl-3(3-methyl-but-2-enyl)quinoline



$C_{17}H_{21}NO_2$
Mol. Wt: 271.4

$C_{16}H_{19}NO_2$
Mol. Wt: 257.3

Sodium hydride (0.70 g of a 60% mineral oil dispersion, 18 mmol) was suspended in DMF (20 ml) and 2-propanethiol (0.57 g, 7.5 mmol) was added. The mixture

was stirred for 5 minutes. A solution of 2,4-dimethoxy-8-methyl-3-(3-methylbut-2-enyl)quinoline (**EXAMPLE 23**) (0.80 g, 3.0 mmol) in DMF (10 ml) was added, followed by heating under reflux for 3 hours. After cooling the reaction mixture was neutralised with 2M hydrochloric acid, and then extracted with ether (3 x 50 ml). The ether layers were dried over $MgSO_4$ and the solvent was evaporated to give a brown oil. Column chromatography (4:1 hexane:EtOAc) yielded 0.3 g, 39% of the product as a yellow solid. Melting point: 164-166°C.

Found M^+: 257.1418 . $C_{16}H_{19}NO_2$ requires 257.1416.

δ_H : 7.82 (1H, d, *J* 8.1, H5), 7.42 (1H, d, *J* 7.0, H7), 7.22 (1H, dd, *J* 8.1, 7.0, H6), 6.59 (1H, br s, OH), 5.37 (1H, br t, *J* 7.3, =CH), 4.06 (3H, s, OMe), 3.51 (2H, d, *J* 7.3, CH_2), 2.66 (3H, s, 8-Me), 1.86 (3H, s, $=CCH_3$), 1.80 (3H, d, *J* 0.9, $=CCH_3$)

δ_C: 160.0, 158.5 (C2, C4), 144.0 (C8a), 137.0, 134.9 (C8 and $=\underline{C}Me_2$), 129.4, 122.7, 121.1, 118.9 (C5, C6, C7 and C=CH), 118.0 (C4a), 104.4 (C3), 53.5 (OMe), 25.9 (8-Me), 22.9 (CH_2), 18.1 (Me), 17.8 (Me).

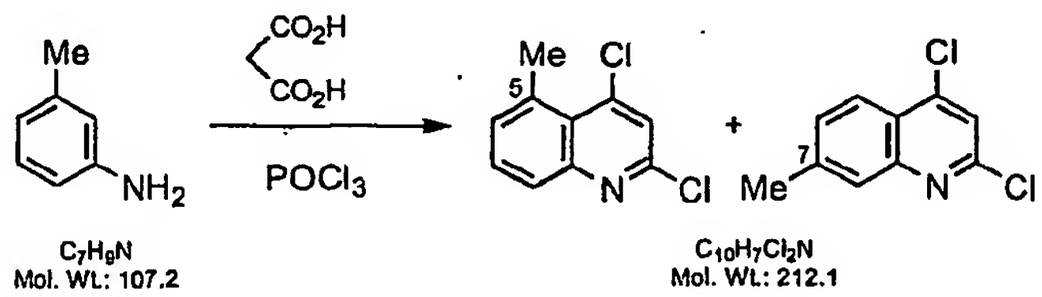
^{1}H NOESY spectrum (DMSO d_6): O<u>H</u> at δ10.2 ppm correlates weakly with H5 at δ8.0 ppm.

n_{max} /cm^{-1}: 3445 (m, O-H), 1619, 1586, (s, C=C, C=N).

m/z: 257 (100%, M^+), 242 (41%, M^+ - Me), 240 (55%), 202 (92%, M^+ - Me_2C=CH).

<u>EXAMPLE 25A. 2,4-Dichloro-5-methylquinoline and</u>

<u>EXAMPLE 25B. 2,4-dichloro-7-methylquinoline</u>



C_7H_9N
Mol. Wt: 107.2

$C_{10}H_7Cl_2N$
Mol. Wt: 212.1

m-Toluidine (5.0 g, 47 mmol) and malonic acid (7.3 g, 70 mmol) were heated under reflux in phosphorus oxychloride (40 ml) for 5 hours, yielding the crude product as an ochre solid after aqueous workup. Continuous (Soxhlet) extraction

with hexane furnished 7.7 g, 77% of a mixture of the two isomeric products; R_f (9:1 hexane:EtOAc) 0.53, one spot. The mixture was used in the next step without separation of isomers.

Found M^+: 210.9954. $C_{10}H_7{}^{35}Cl_2N$ requires 210.9955.

n_{max} /cm^{-1}: 1569 (m, C=C or C=N).

m/z: 215 (55%, M^+, $^{37}Cl_2$), 213 (93%, M^+, $^{37}Cl^{35}Cl$), 211 (100%, M^+, $^{35}Cl_2$), 176 (85%, M^+ - Cl), 140 (84%, M^+ - 2Cl, H).

^1H NMR showed the two products in a 7:5 ratio of 5-methyl:7-methyl:

5-Methyl isomer (EXAMPLE 25A)

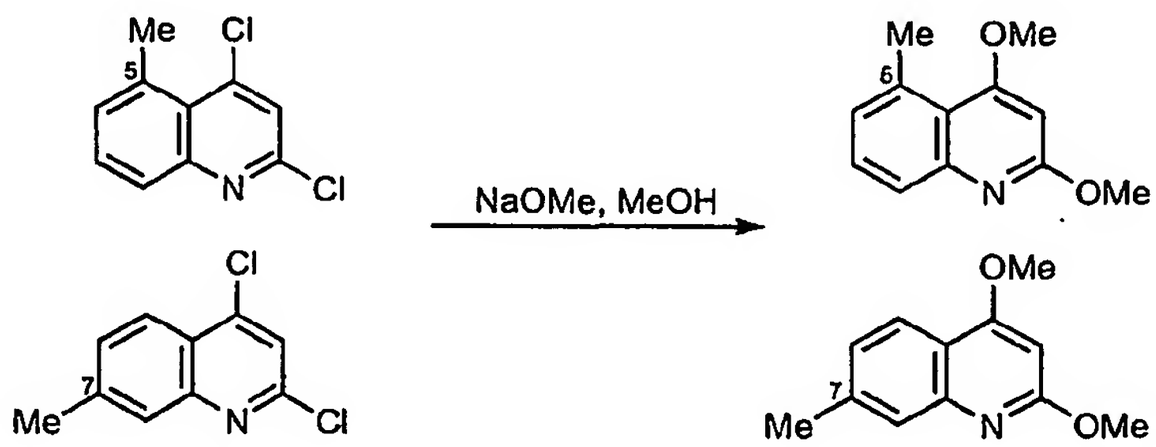
δ_H: 7.87 (1H, dd, *J* 7.3, 0.6, H8), 7.58 (1H, dd, *J* 8.2, 7.3, H7), 7.41 (1H, s, H3), 7.35 (1H, dd, *J* 8.2, 0.6, H6), 2.99 (3H, s, 5-Me).

7-Methyl isomer (EXAMPLE 25B)

δ_H: 8.02 (1H, d, *J* 8.5, H5), 7.77 (1H, d, *J* 1.0, H8), 7.44 (1H, dd, *J* 8.5, 1.0, H6), 7.40 (1H, s, H3), 2.56 (3H, s, 7-Me).

EXAMPLE 26A. 2,4-Dimethoxy-5-methylquinoline and

EXAMPLE 26B. 2,4-dimethoxy-7-methylquinoline



$C_{10}H_7Cl_2N$
Mol. Wt.: 212.1

$C_{12}H_{13}NO_2$
Mol. Wt.: 203.2

The isomeric mixture of 2,4-dichloromethylquinolines (4.0 g, 19 mmol) was heated under reflux in sodium methoxide (2.0 g Na in 75 ml MeOH) for 50 hours, then cooled, poured into cold water and filtered under suction to give the product as an off-white powder, yield 2.9 g, 75%. R_f (9:1 hexane:EtOAc) 0.39, broad spot. The mixture was used in the next step.

Found M^+: 203.0959. $C_{12}H_{13}NO_2$ requires 203.0946.

n_{max} /cm^{-1}: 1612, 1590 (s, C=C, C=N), 1207 (s, C-O-C).

m/z: 203 (100%, M^+), 202 (75%, M^+ - H), 173 (26%, M^+ - 2Me).

^1H NMR of mixture showed the two isomers in the ratio 11:10 5-methyl:7-methyl.

5-Methyl isomer (EXAMPLE 26A)

δ_H: 7.61 (1H, d, *J* 8.3, H8), 7.41 (1H, dd, *J* 8.3, 7.2, H7), 7.06 (1H, d, *J* 7.2, H6), 6.17 (1H, s, H3), 4.03 (3H, s, OMe), 3.90 (3H, s, OMe), 2.78 (3H, s, 5-Me).

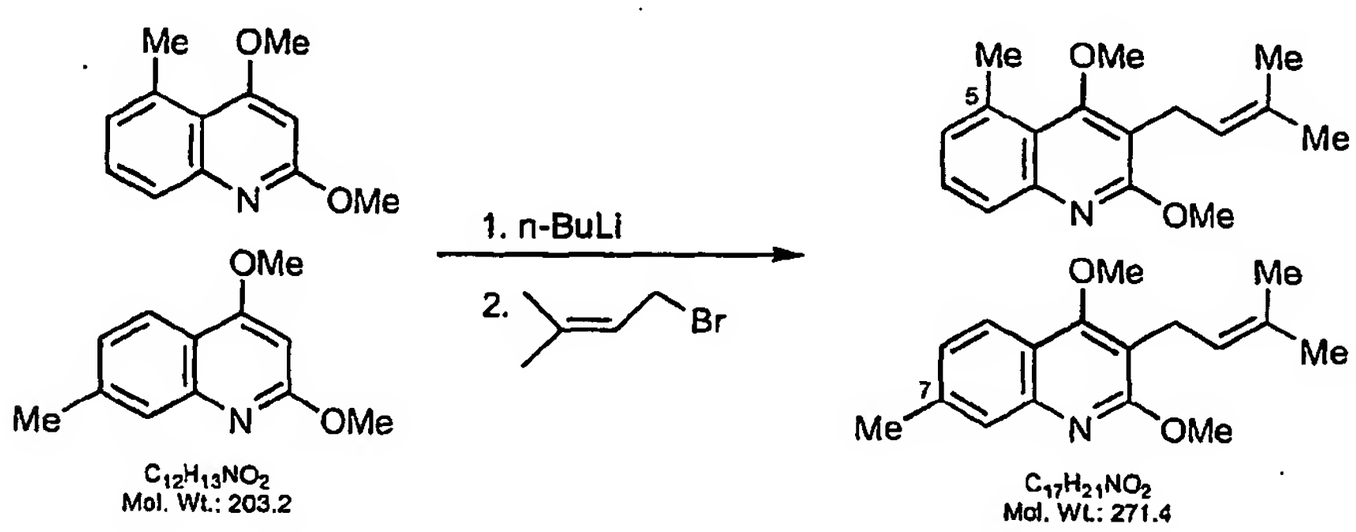
7-Methyl isomer (EXAMPLE 26B)

δ_H: 7.92 (1H, d, *J* 8.3, H5), 7.58 (1H, d, *J* 0.6, H8), 7.15 (1H, dd, *J* 8.3, 0.6, H6), 6.15 (1H, s, H3), 4.04 (3H, s, OMe), 3.96 (3H, s, OMe), 2.49 (3H, s, 7-Me)

EXAMPLE 27A. 2,4-Dimethoxy-5-methyl-3-(3-methylbut-2-enyl)quinoline

and

EXAMPLE 27B. 2,4-dimethoxy-7-methyl-3-(3-methylbut-2-enyl)quinoline



$C_{12}H_{13}NO_2$
Mol. Wt.: 203.2

$C_{17}H_{21}NO_2$
Mol. Wt.: 271.4

The isomeric 2,4-dimethoxyquinoline mixture (2.0 g, 9.9 mmol) was dissolved in THF (40 ml) and cooled to 0°C. *n*-Butyllithium (6.0 ml of 2.5M solution, 15 mmol) was added dropwise, and the deep red solution was stirred at 0°C for 30 minutes. 1-Bromo-3-methylbut-2-ene (2.7 g, 18 mmol) was added slowly, and the mixture stirred for 1 hour whilst slowly warming to room temperature. The mixture was poured into cold water, extracted with ether (3 x 30 ml), dried, and the solvent removed to give the product as a brown oil. Yield 1.46 g, 54%. R_f (9:1

hexane:EtOAc) 0.52, broad single spot. The mixture was used in the next step without further purification.

Found M^+: 271.1572 . $C_{17}H_{21}NO_2$ requires 271.1572.

n_{max} /cm^{-1}: 2946 (s, C-H), 1606, 1580 (s, C=N, C=C)

m/z: 271 (91%, M^+), 256 (76%, M^+ - Me), 202 (27%, $C_{12}H_{12}NO_2^+$), 51 (100%).

^1H NMR spectrum showed the two isomers in a 5:4 ratio; some signals coincident.

5-Methyl isomer (EXAMPLE 27A)

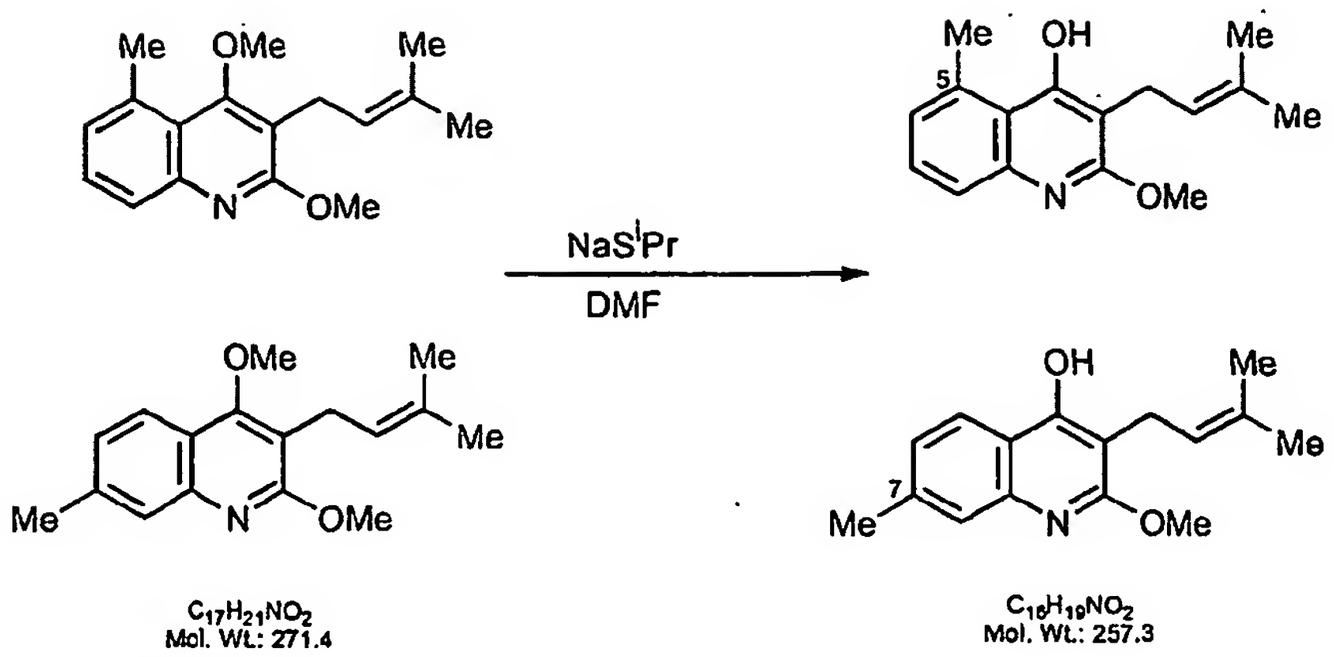
δ_H: 7.66 (1H, d, *J* 8.2, H8), 7.39 (1H, d, *J* 8.2, 7.2, H7), 7.08 (1H, d, *J* 7.2, H6), 5.27-5.20 (1H, m, $Me_2C=C\underline{H}$), 4.06, (3H, s, OMe), 3.76 (3H, s, OMe), 3.45-3.42 (2H, m, Ar-CH_2), 2.80 (3H, s, 5-Me), 1.80 (3H, s, Me), 1.69 (3H, s, Me).

7-Methyl isomer (EXAMPLE 27B)

δ_H: 7.78 (1H, d, *J* 8.3, H5), 7.62 (1H, s, H8), 7.17 (1H, d, *J* 8.3, H6), 5.27-5.20 (1H, m, $Me_2C=C\underline{H}$), 4.06, (3H, s, OMe), 3.91 (3H, s, OMe), 3.45-3.42 (2H, m, Ar-CH_2), 2.48 (3H, s, 7-Me), 1.80 (3H, s, Me), 1.69 (3H, s, Me).

EXAMPLE 28A. 4-Hydroxy-2-methoxy-5-methyl-3-(3-methylbut-2-enyl)quinoline and

EXAMPLE 28B. 4-Hydroxy-2-methoxy-7-methyl-3-(3-methylbut-2-enyl)quinoline



$C_{17}H_{21}NO_2$
Mol. Wt: 271.4

$C_{16}H_{19}NO_2$
Mol. Wt.: 257.3

Sodium hydride (0.85 g of a 60% dispersion in mineral oil, 21 mmol) was washed with hexane under argon, and then suspended in dry DMF (30 ml). 2-Propanethiol (0.68 g, 9.0 mmol) was added, and the mixture stirred for 5 minutes. The mixture of isomers **28A** and **28B** (1.0 g, 3.7 mmol) was then added, and the mixture heated under reflux for 3 hours. After aqueous workup as for previous demethylations the crude product was obtained as a yellow solid. Tlc showed 2 spots, R_f 0.30 and 0.40 (6:1 hexane:EtOAc). Column chromatography (6:1) yielded the two isomeric products, R_f 0.40 and R_f 0.30. NMR identified the higher R_f component as the 5-methyl isomer and the other as the 7-methyl isomer.

Data for 4-hydroxy-2-methoxy-5-methyl-3-(3-methylbut-2-enyl)quinoline (EXAMPLE 28A)

Bright yellow solid, R_f (6:1 hexane:EtOAc) 0.40. Yield 0.1g. Melting point 118-120°C.

Found M^+: 257.1425. $C_{16}H_{19}NO_2$ requires 257.1416.

δ_H: 7.47 (1H, d, *J* 8.2, H8), 7.24 (1H, m, H7), 6.91 (1H, d, *J* 7.0, H6), 5.14 (1H, br t, C=C<u>H</u>), 3.95 (3H, s, OMe), 3.32 (2H, d, *J* 6.3, CH_2), 2.76 (3H, s, 5-Me), 1.69 (3H, s, CH_3), 1.63 (3H, s, CH_3).

δ_C: 160.3 (C2), 145.5 (C8a), 136.5, 135.8 (C5 and =$\underline{C}Me_2$), 129.3, 126.6, 123.3, 121.9 (C6, C7, C8 and C=$\underline{C}$H), 119.4 (C4a), 106.3 (C3), 55.0 (OMe), 26.2 (Me), 24.5 (Me), 22.8 (CH_2), 18.3 (Me). No signal was observed for C4.

n_{max} /cm^{-1}: 3400 (br, OH), 1617, 1584, 1561 (s, C=C, C=N).

m/z: 257 (100%, M^+), 242 (20%, M^+ - Me), 202 (64%, M^+ - CH=$C(Me)_2$).

Data for 4-hydroxy 2-methoxy 7-methyl 3-(3-methylbut-2-enyl)quinoline (EXAMPLE 28B)

Off-white powder, R_f (6:1 hexane:EtOAc) 0.30. Yield 0.15g. Melting point 149-151°C.

Found M^+: 257.1412.. $C_{16}H_{19}NO_2$ requires 257.1416.

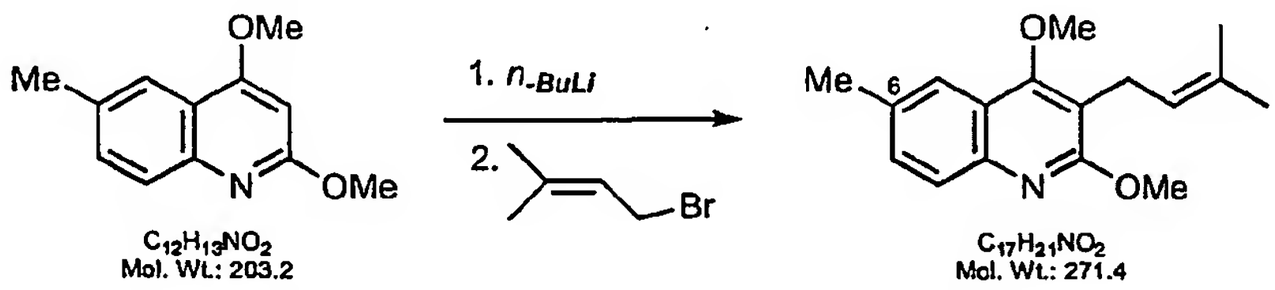
δ_H: 7.88 (1H, d, *J* 8.3, H5), 7.55 (1H, s, H8), 7.14 (1H, d, *J* 8.3, H6), 5.36 (1H, t, *J* 7.2, =CH), 4.04 (3H, s, OMe), 3.48 (2H, d, *J* 7.2, CH_2), 2.47 (3H, s, 7-Me), 1.84 (3H, s, CH_3), 1.79 (3H, s, CH_3).

δ_C: 161.9 (C2), 139.9, 136.8 (C8a and C7), 128.7 (CH), 127.4 ($Me_2\underline{C}$=), 126.0, 125.5, 121.6 (CH), 117.2 (C4a), 104.7 (C3), 54.3 (OMe), 26.2 (Me), 23.6 (CH_2), 22.1 (Me), 18.4 (Me). No signal was observed for C4.

n_{max} /cm^{-1}: 3200 (m, O-H), 1635, 1576, (s, C=C, C=N).

m/z: 257 (100%, M^+), 242 (39%, M^+ - Me), 202.1 (56%, M^+ - CH=$C(Me)_2$).

EXAMPLE 29. 2,4-Dimethoxy-6-methyl-3-(3-methyl-2-butenyl)quinoline



$C_{12}H_{13}NO_2$
Mol. Wt: 203.2

$C_{17}H_{21}NO_2$
Mol. Wt: 271.4

2,4-Dimethoxy-6-methylquinoline (**EXAMPLE 11**) (0.80 g, 4.0 mmol) was dissolved in dry THF (20 ml) and cooled to 0°C, with stirring. *n*-Butyllithium (3.7 ml of a 1.6M solution in hexanes) was added dropwise, and the mixture stirred at 0°C for 40 minutes. 1-Bromo-3-methyl-2-butene (1.2 g, 8.1 mmol) was then added, and the resultant brown solution allowed to warm to room temperature

over a period of 1 hour. The mixture was poured into cold water, and extracted with diethyl ether (3 x 30 ml). The combined organic extracts were dried over $MgSO_4$, and the solvent removed *in vacuo* to give the crude product as a brown liquid. Column chromatography (9:1 hexane:EtOAc) yielded the title compound as a pale brown oil, R_f 0.70. Yield 0.78 g, 73%.

Found M^+: 272.1638. $C_{17}H_{22}NO_2$ requires 272.1651.

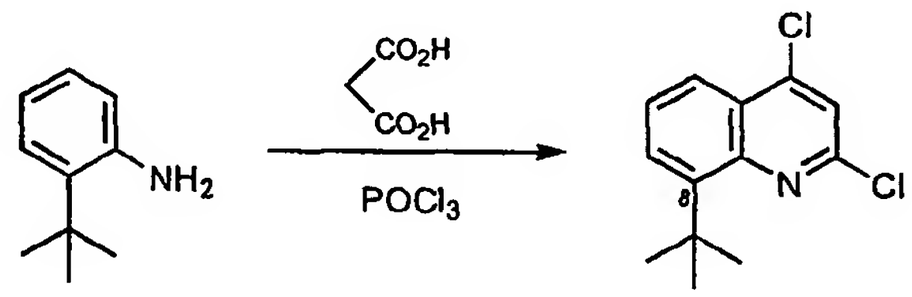
δ_H: 7.71 (1H, d, *J* 8.5, H8), 7.67 (1H, d, *J* 1.9, H5), 7.38 (1H, dd, *J* 8.5, 1.9, H7), 5.22 (1H, t, *J* 6.9, $Me_2C=C\underline{H}$), 4.06 (3H, s, OMe), 3.93 (3H, s, OMe), 3.43 (2H, d, *J* 6.9, CH_2), 2.49 (3H, s, 6-Me), 1.81 (3H, s, Me), 1.68 (3H, s, Me).

δ_C: 162.0, 161.1 (C2, C4), 144.4 (C8a), 133.1, 132.1 (C6 and $C=\underline{C}Me_2$), 130.8, 127.0, 121.9, 121.0 (C5, C7, C8, $C=\underline{C}H$), 120.8 (C4a), 116.7 (C3), 62.1 (OMe), 53.6 (OMe), 25.7 (Me), 23.2 (CH_2), 21.6 (Me), 17.9 (Me).

n_{max} /cm^{-1}: 2926 (s, C-H), 1609, 1572 (s, C=C, C=N).

m/z: 272 (100%, M^+), 271 (52%, M^+ - H), 270 (51%, M^+ - 2H), 216 (33%, $C_{13}H_{14}NO_2^+$).

EXAMPLE 30. 8-*tert*-Butyl-2,4-dichloroquinoline



$C_{10}H_{15}N$
Mol. Wt.: 149.2

$C_{13}H_{13}Cl_2N$
Mol. Wt.: 254.2

2-*tert*-Butylaniline (7.0 g, 47 mmol) and malonic acid (7.3 g, 70 mmol) were heated under reflux in phosphorus oxychloride (40 ml) for 6 hours. Continuous hexane extraction of the crude product obtained after aqueous alkaline workup yielded a brown oil. Tlc (95:5 hexane:EtOAc) showed 3 spots; R_f 0.75, 0.12, baseline. Column chromatography (95:5 hexane:EtOAc) furnished the pure quinoline (R_f 0.75) as yellow plates. Yield 1.0 g, 8%. Melting point 56-58°C.

Found M^+: 253.0121. $C_{13}H_{13}{}^{35}Cl_2N$ requires 253.0425.

δ_H: 8.09 (1H, dd, *J* 8.3, 1.3, H5), 7.75 (1H, dd, *J* 7.5, 1.3, H7), 7.51 (1H, dd, *J* 8.3, 7.5, H6), 7.46 (1H, s, H3), 1.64 (9H, s, ^{t}Bu).

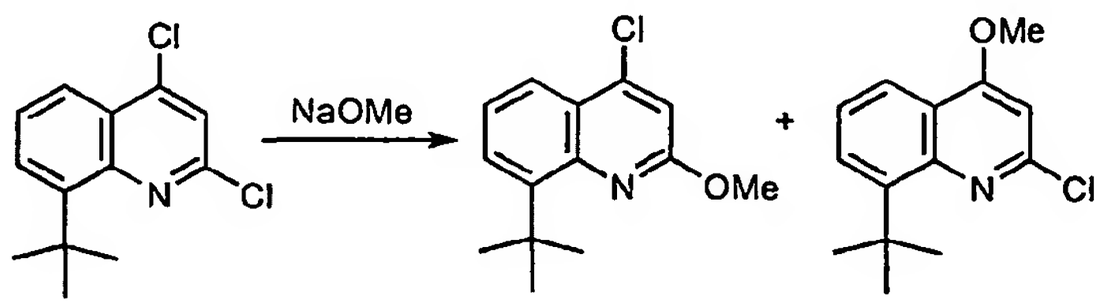
δ_C: 148.2, 147.0, 146.3, 144.5 (C2, C4, C8, C8a), 128.3, 127.4, 126.2 (C4a), 122.7, 121.2, 36.7 ($\underline{C}Me_3$) 31.1 ($(CH_3)_3$).

n_{max} /cm^{-1}: 1578, 1562 (s, C=N, C=C)

m/z: 257 (6%, M^+ $^{37}Cl_2$), 253 (41%, M^+ $^{35}Cl_2$), 238 (89%, M^+ $^{35}Cl_2$ - Me), 211 (100%, M^+ - C_3H_6).

EXAMPLE 31A. 8-*tert*-Butyl-2-chloro-4-methoxyquinoline and

EXAMPLE 31B. 8-*tert*-butyl-4-chloro-2-methoxyquinoline



$C_{13}H_{13}Cl_2N$
Mol. Wt.: 254.2

$C_{14}H_{16}ClNO$
Mol. Wt.: 249.7

8-*tert*-Butyl-2,4-dichloroquinoline (**EXAMPLE 30**) (0.7 g, 2.8 mmol) was heated under reflux in methanolic sodium methoxide (1.0 g Na in 50 ml MeOH) for 80 hours. Tlc showed a mixture of products, R_f (hexane) 0.48, 0.22. Column chromatography (hexane) yielded the two isomeric chloromethoxyquinolines as white needles.

Data for 8-*tert*-butyl-4-chloro-2-methoxyquinoline (EXAMPLE 31A)

Yield 0.11g, 16%. R_f (hexane) 0.48. Melting point 54-56°C.

Found M^+: 249.0917. $C_{14}H_{16}{}^{35}ClNO$ requires 249.0920.

δ_H: 8.03 (1H, dd, *J* 8.2, 1.4, H5), 7.67 (1H, dd, *J* 7.5, 1.4, H7), 7.38 (1H, dd, *J* 8.2, 7.5, H6), 7.02 (1H, s, H3), 4.07 (3H, s, OMe), 1.65 (9H, s, ^{t}Bu).

δ_C: 159.1 (C2), 146.2, 145.6, 144.3 (C4, C8, C8a), 127.6, 124.4, 124.1 (C4a), 122.7, 111.8 (C3), 54.2 (OMe), 36.4 ($\underline{C}Me_3$), 30.5 ($(CH_3)_3$).

n_{max} /cm^{-1}: 1608, 1574 (s, C=C, C=N).

m/z: 251 (16%, M^+ ^{37}Cl), 250 (16%, M^+ ^{37}Cl - H), 249 (48%, M^+ ^{35}Cl), 248 (27%, M^+ ^{35}Cl - H), 236 (33%, M^+ ^{37}Cl - Me), 234 (100%, M^+ ^{35}Cl - Me), 209 (34%, M^+ ^{37}Cl - C_3H_6), 207 (72%, M^+ - C_3H_6).

Data for 8-*tert*-butyl-2-chloro-4-methoxyquinoline (EXAMPLE 31B)

Yield 0.20g, 29%. R_f (hexane) 0.22. Melting point 96-98°C. (Found C: 67.71, H: 6.75, N: 5.32%. $C_{14}H_{16}ClNO$ requires C: 67.33, H: 6.46, N: 5.61%.)

Found M^+: 249.0917. $C_{14}H_{16}{}^{35}ClNO$ requires 249.0920.

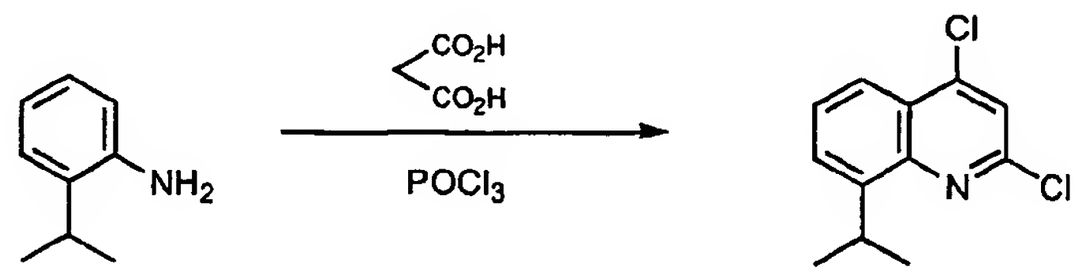
δ_H: 8.02 (1H, dd, *J* 8.2, 1.4, H5), 7.66 (1H, dd, *J* 7.5, 1.4, H7), 7.40 (1H, dd, *J* 8.2, 7.5, H6), 6.69 (1H, s, H3), 4.01 (3H, s, OMe), 1.63 (9H, s, ^tBu).

δ_C: 163.9 (C4), 148.0, 147.1, 146.9 (C2, C8, C8a), 127.5, 125.5, 121.4 (C4a), 120.3, 100.4 (C3), 56.1 (OMe), 36.5 ($\underline{C}Me_3$), 31.0 ((CH_3)$_3$).

ν_{max} /cm^{-1}: 1588, 1575 (s, C=C, C=N)

m/z: 251 (11%, M^+ ^{37}Cl), 250 (15%, M^+ ^{37}Cl - H), 249 (35%, M^+ ^{35}Cl), 248 (28%, M^+ ^{35}Cl - H), 236 (29%, M^+ ^{37}Cl - Me), 234 (85%, M^+ ^{35}Cl - Me), 209 (34%, M^+ ^{37}Cl - C_3H_6), 207 (100%, M^+ ^{35}Cl - C_3H_6).

EXAMPLE 32. 2,4-Dichloro-8-isopropylquinoline



$C_9H_{13}N$
Mol. Wt.: 135.2

$C_{12}H_{11}Cl_2N$
Mol. Wt.: 240.1

2-Isopropylaniline (7.0 g, 52 mmol) and malonic acid (8.1 g, 78 mmol) were heated under reflux in phosphorus oxychloride (40 ml) for 6 hours. Standard aqueous workup gave the crude product as a brown solid. Soxhlet extraction (hexane, 4h) of the crude yielded the pure product as a colourless oil. Yield 3.3 g, 26%.

Found M^+: 239.0250. $C_{12}H_{11}{}^{35}Cl_2N$ requires 239.0269.

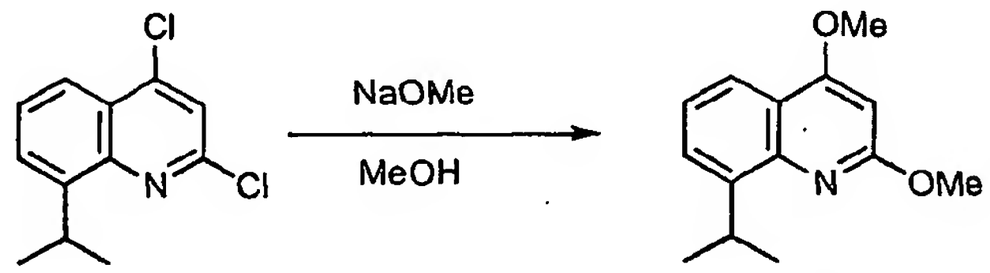
δ_H: 8.00 (1H, dd, *J* 8.3, 1.4, H5), 7.66 (1H, dd, *J* 7.3, 1.4, H7), 7.57 (1H, dd, *J* 8.3, 7.3, H6), 7.45 (1H, s, H3), 4.22 (1H, septet, *J* 6.9, C<u>H</u>Me_2), 1.34 (6H, d, *J* 6.9, ($C\underline{H}_3$)$_2$).

δ_C: 148.5, 147.4, 146.2, 144.5 (C2, C4, C8, C8a), 127.8, 127.4, 125.3 (C4a), 121.8, 121.6, 27.5 (<u>C</u>HMe_2), 23.6 ((CH_3)$_2$).

n_{max} /cm^{-1}: 1607, 1564 (s, C=N, C=C).

m/z: 241 (26%, M^+ $^{37}Cl^{35}Cl$), 239 (42%, M^+ $^{35}Cl_2$), 226 (57%, M^+ $^{37}Cl^{35}Cl$ - CH_3), 211 (36%, M^+ - C_2H_4).

EXAMPLE 33. 2,4-Dimethoxy-8-isopropylquinoline



$C_{12}H_{11}Cl_2N$
Mol. Wt: 240.1

$C_{14}H_{17}NO_2$
Mol. Wt: 231.3

2,4-Dichloro-8-isopropylquinoline (**EXAMPLE 32**) (2.0 g, 8.3 mmol) was heated under reflux in methanolic sodium methoxide (1.5 g Na in 75 ml MeOH) for 48 hours, then cooled and poured into cold water. The product was obtained by filtration as white needles. Yield 1.1 g, 57%. Melting point 57-59°C.

Found M^+: 231.1252. $C_{14}H_{17}NO_2$ requires 231.1259.

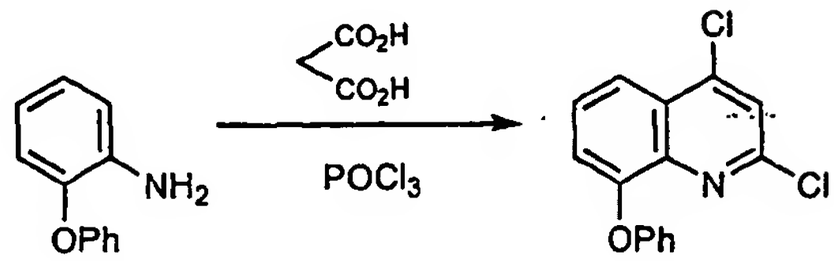
δ_H: 7.95 (1H, dd, *J* 8.2, 1.5, H5), 7.55 (1H, dd, *J* 7.4, 1.5, H7), 7.34 (1H, dd, *J* 8.2, 7.4, H6), 6.26 (1H, s, H3), 4.19 (1H, septet, *J* 6.9, ArC<u>H</u>(Me_2), 4.10 (3H, s, OMe), 3.99 (3H, s, OMe), 1.42 (6H, d *J* 6.9, CH($C\underline{H}_3$)$_2$).

δ_C: 164.3, 162.4 (C2, C4), 145.0, 144.7 (C8, C8a), 125.8, 123.1, 119.3 (C5, C6, C7), 119.1 (C4a), 90.1 (C3), 55.7 (OMe), 53.2 (OMe), 28.1 (<u>C</u>HMe_2), 23.1 ((CH_3)$_2$).

n_{max} /cm^{-1}: 1619, 1602, 1586 (s, C=C, C=N).

m/z: 231 (73%, M^+), 230 (56%, M^+ - H), 216 (100%, M^+ - Me), 203 (44%), 189 (26%).

EXAMPLE 34. 2,4-Dichloro-8-phenoxyquinoline



$C_{12}H_{11}NO$
Mol. Wt: 185.2

$C_{15}H_9Cl_2NO$
Mol. Wt: 290.1

2-Phenoxyaniline (3.9 g, 21 mmol), malonic acid (3.3 g, 32 mmol) and phosphorus oxychloride (30 ml) were heated under reflux for 6 hours. Standard aqueous workup gave a brown solid, which was extracted continuously with hexane for 5 hours to give a dark orange solid. Further purification by column chromatography (9:1 hexane:EtOAc) was necessary to yield the pure product (R_f 0.65) as yellow needles. Yield 2.2 g, 36%. Melting point 90-92°C.

Found M^+: 289.0041. $C_{15}H_9{}^{35}Cl_2NO$ requires 289.0061.

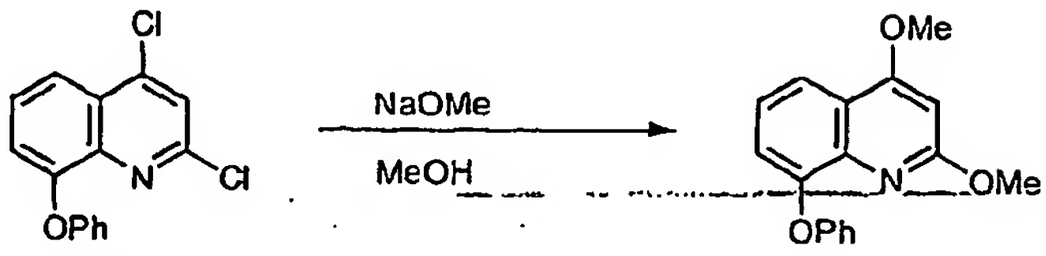
δ_H: 7.88 (1H, dd, *J* 8.4, 1.2, H5), 7.57 (1H, s, H3), 7.49 (1H, dd, *J* 8.4, 7.9, H6), 7.42-7.37 (2H, m, H2' and H6'), 7.19 (1H, tt, *J* 7.4, 1.1, H4'), 7.16-7.12 (2H, m, H3' and H5'), 7.08 (1H, dd, *J* 7.9, 1.2, H7).

δ_C: 156.4 (C2), 154.0 (C4), 149.7 (C8a), 144.4, 140.6 (C1' and C8), 130.0 (ArH), 127.9 (ArH), 126.7 (C4a), 124.5 (ArH), 123.0 (ArH), 120.5 (ArH), 118.1 (ArH), 116.9 (ArH).

n_{max}/cm^{-1}: 1590, 1572 (s,.C=N, C=C).

m/z: 293 (27%, $M^+ {}^{37}Cl_2$), 292 (18%, $M^+ {}^{37}Cl_2$ - H), 291 (46%, $M^+ {}^{37}Cl^{35}Cl$), 290 (77%, $M^+ {}^{37}Cl^{35}Cl$ - H), 289 (70%, $M^+ {}^{35}Cl_2$), 288 (100%. $M^+ {}^{35}Cl_2$ - H), 209 (27%).

EXAMPLE 35. 2,4-Dimethoxy-8-phenoxyquinoline



$C_{15}H_9Cl_2NO$
Mol. Wt: 290.1

$C_{17}H_{15}NO_3$
Mol. Wt: 281.3

2,4-Dichloro-8-phenoxyquinoline (**EXAMPLE 34**) (0.70 g, 2.4 mmol) was heated under reflux in excess methanolic sodium methoxide (from 1.0 g Na in 60 ml MeOH) for 48 hours. The mixture was poured into cold water, left to stand for 1 hour and then filtered to give the title compound as a yellow powder. Yield 0.50 g, 74%. Melting point 90-92°C.

Found M^+: 281.1065. $C_{17}H_{15}NO_3$ requires 281.1052.

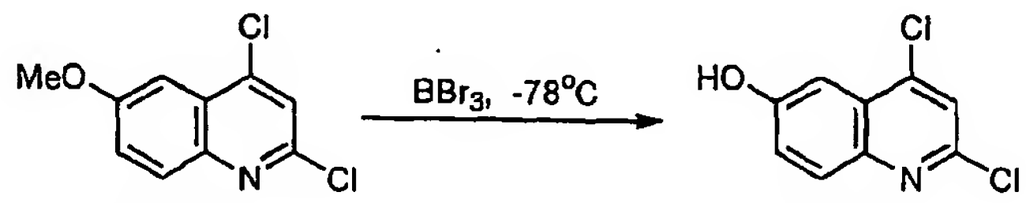
δ_H: 7.87 (1H, dd, *J* 7.9, 1.5, H5), 7.35-7.23 (4H, m, ArH), 7.02-6.95 (3H, m, ArH), 6.20 (1H, s, H3), 3.98 (3H, s, OMe), 3.72 (3H, s, OMe).

δ_C: 164.0, 163.2, 159.3, 150.4 (C2, C4, C8, C1'), 140.0 (C8a), 129.3 (ArH), 123.1 (ArH), 121.9 (ArH), 121.1 (C4a), 120.9 (ArH), 118.0 (ArH), 117.3 (ArH), 91.0 (C3), 53.9 (OMe), 53.4 (OMe).

n_{max}/cm^{-1}: 3066 (m, Ar-H), 1623, 1603, 1583 (s, C=C, C=N), 1249, 1211, 1060 (s, C-O-C)

m/z: 281 (100%, M^+), 280 (68%, M^+ - H), 269 (21%), 201 (19%), 169 (23%), 151 (40%).

EXAMPLE 36. 2,4-Dichloro-6-hydroxyquinoline



$C_{10}H_7Cl_2NO$
Mol. Wt: 228.1

$C_9H_5Cl_2NO$
Mol. Wt: 214.1

2,4-Dichloro-6-methoxyquinoline (**EXAMPLE 14**) (2.0 g, 8.8 mmol) was dissolved in dry dichloromethane (80 ml) and cooled to -78°C. Boron tribromide (10 ml of a 1M solution in dichloromethane, 10 mmol) was added dropwise over 15 minutes, with stirring. The reaction mixture was then allowed to attain room temperature overnight before shaking with ice-cold water. An ochre solid was precipitated, which was redissolved by the addition of ether (100 ml). The mixture was then extracted with ether (3 x 75 ml). The combined organic layers were extracted with 2M sodium hydroxide (2 x 30 ml), and then dilute HCl was added to the combined aqueous extracts until a precipitate appeared. Extraction with ether (3 x 75 ml) followed by drying of the ether extracts ($MgSO_4$) and removal of the solvent *in vacuo* yielded the pure quinoline as a pale yellow solid. Yield 1.0 g, 53%. Melting point 182-184°C.

Found M^+: 212.9767. $C_9H_5{}^{35}Cl_2NO$ requires 212.9748.

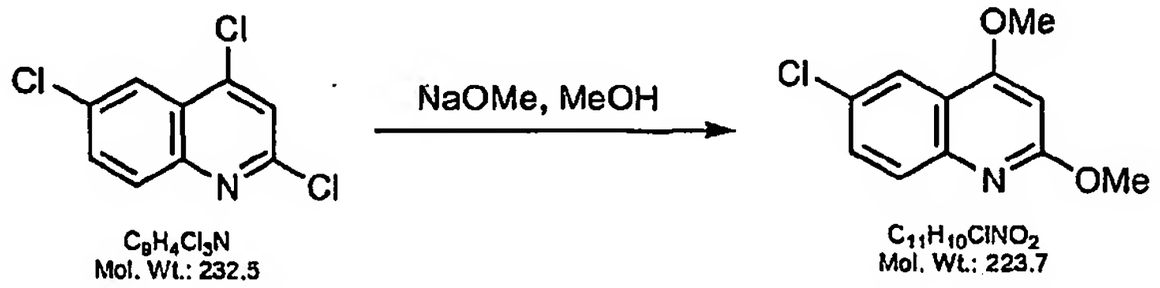
δ_H (DMSO d_6): 10.7 (1H, s, OH), 7.93 (1H, d, *J* 9.1, H8), 7.84 (1H, s, H3), 7.49 (1H, dd, *J* 9.1, 2.6, H7), 7.42 (1H, d, *J* 2.6, H5)

δ_C (DMSO d_6): 157.8, 145.7, 142.7, 141.6 (C2, C4, C6, C8a), 130.7, 126.4 (C4a), 124.5, 122.1, 105.1 (C3).

n_{max} /cm^{-1}: 3200-3000 (m br, OH), 1616, 1560 (s, C=C, C=N).

m/z: 215 (87%, M^+ $^{35}Cl^{37}Cl$), 213 (98%, M^+ $^{35}Cl_2$), 178 (76%, M^+ - Cl), 143 (34%, M^+ - 2Cl).

EXAMPLE 37. 6-Chloro-2,4-dimethoxyquinoline



$C_9H_4Cl_3N$
Mol. Wt.: 232.5

$C_{11}H_{10}ClNO_2$
Mol. Wt.: 223.7

2,4,6-Trichloroquinoline (**EXAMPLE 15**) (1.5 g, 64 mmol) was heated under reflux in excess methanolic sodium methoxide (1.0 g Na in 60 ml MeOH) for 48 hours,

then cooled and poured into cold water. The product was obtained by filtration as white needles.

Yield 1.3 g, 91%. Melting point 47-49°C.

Found M^+: 223.0746. $C_{11}H_{10}{}^{35}ClNO_2$ requires 223.0400.

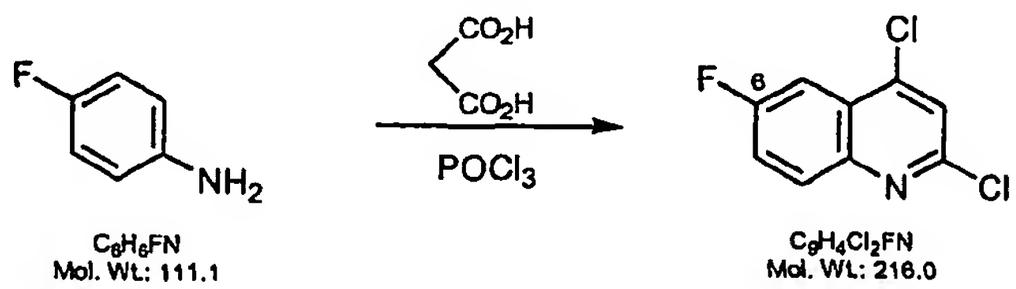
δ_H: 7.93 (1H, d, *J* 2.4, H5), 7.62 (1H, d, *J* 8.9, H8), 7.44 (1H, dd, *J* 8.9, 2.4, H7), 6.14 (1H, s, H3), 3.96 (3H, s, MeO), 3.90 (3H, s, MeO).

δ_C: 164.0 (C2), 163.0 (C4), 145.5 (C8a), 130.5 (C8), 128.9 (C6), 128.4 (C7), 121.2 (C5), 120.0 (C4a), 91.5 (C3), 55.9 (OMe), 53.5 (OMe).

n_{max} /cm^{-1}: 1622, 1601, 1576 (s, C=C, C=N), 1208 (s, C-O).

m/z: 225 (38%, M^+ ^{37}Cl), 224 (28%, M^+ ^{37}Cl - H), 223 (100%, M^+ ^{35}Cl), 222 (53%, M^+ ^{35}Cl - H), 193 (20%), 162 (13%), 151 (17%).

EXAMPLE 38. 2,4-Dichloro-6-fluoroquinoline



C_6H_6FN
Mol. Wt: 111.1

$C_9H_4Cl_2FN$
Mol. Wt: 216.0

4-Fluoroaniline (7.0 g, 63 mmol), malonic acid (9.8 g, 94 mmol) and phosphorus oxychloride (60 ml) were heated under reflux for 6 hours, then poured into crushed ice and made alkaline with aqueous NaOH. Filtration gave the crude product as a brown solid, which was continuously extracted (hexane, 4 h) to yield the title compound as a pale yellow powder. Yield 5.2 g, 38%. Melting point 90-92°C. (Found C: 49.98, H: 1.57, N: 6.23%. $C_9H_4Cl_2FN$ requires C: 50.04, H: 1.87, N: 6.48%.)

Found M^+: 214.9703. $C_9H_4{}^{35}Cl_2FN$ requires 214.9705.

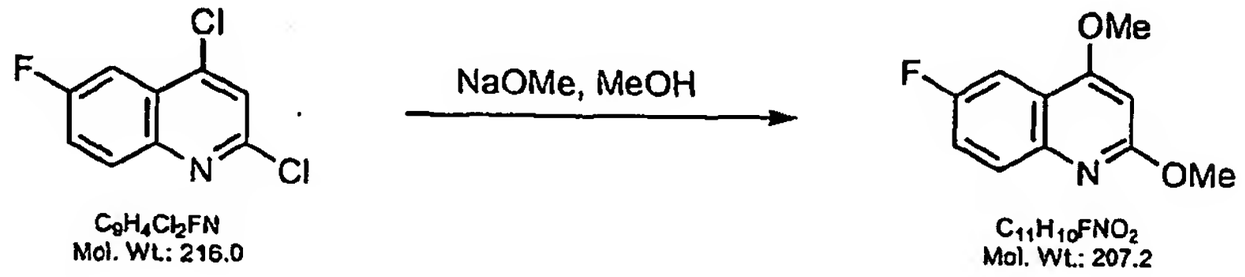
δ_H: 8.04 (1H, dd, *J* 9.3, 5.1(J_{H-F}), H8), 7.80 (1H, dd, *J* 9.1(J_{H-F}), 2.8, H5), 7.56 (1H, ddd, *J* 9.3, 8.0 (J_{H-F}), 2.8, H7), 7.53 (1H, s, H3).

δ_C: 161.3 (d, J_{C-F} 251, C6), 149.3 (C2), 145.1 (C4), 143.6 (d, J_{C-F} 5.5, C8a), 131.7 (d, J_{C-F} 9.2, C8), 126.3 (d, J_{C-F} 10.4, C4a), 122.7 (C3), 121.7 (d, J_{C-F} 25.7, C7), 108.3 (d, J_{C-F} 24.9, C5).

n_{max} /cm^{-1}: 1620, 1580 (s, C=C, C=N).

m/z: 217 (79%, M^+ $^{35}Cl^{37}Cl$), 215 (100%, M^+ $^{35}Cl_2$), 180 (54%, M^+ - Cl), 145 (30%, M^+ - 2Cl).

EXAMPLE 39. 2,4-Dimethoxy-6-fluoroquinoline



$C_9H_4Cl_2FN$
Mol. Wt.: 216.0

$C_{11}H_{10}FNO_2$
Mol. Wt.: 207.2

2,4-Dichloro-6-fluoroquinoline (**EXAMPLE 38**) (3.5 g, 16.2 mmol) was heated under reflux in excess sodium methoxide (2.0 g Na in 100 ml MeOH) for 24 hours. After aqueous work up the product was obtained as off-white needles, R_f (4:1 hexane:EtOAc) 0.50. Yield 2.5 g, 75%. Melting point 74-77°C.

Found M^+: 207.0692. $C_{11}H_{10}FNO_2$ requires 207.0696.

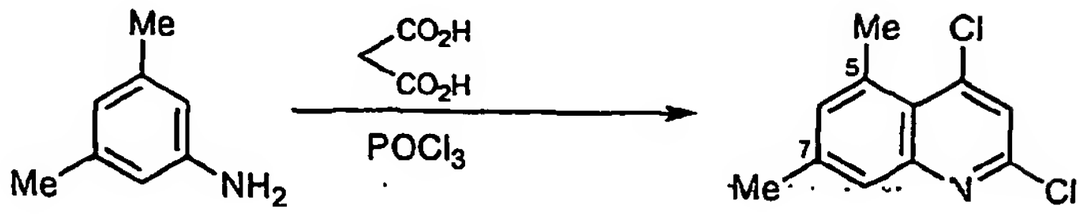
δ_H: 7.74 (1H, dd, *J* 9.1, 5.2 (J_{H-F}), H8), 7.65 (1H, dd, *J* 9.5(J_{H-F}), 3.0, H5), 7.34 (1H, ddd, *J* 9.1, 8.3(J_{H-F}), 3.0, H7), 6.22 (1H, s, H3), 4.03 (3H, s, OMe), 3.97 (3H, s, OMe).

δ_C: 163.4 (C2/C4), 158.8 (d, J_{C-F} 242.2, C6), 143.8 (C8a), 128.8 (d, J_{C-F} 8.5, C8), 119.7 (d, J_{C-F} 9.0, C4a), 119.1 (d, J_{C-F} 24.8, C7), 106.2 (d, J_{C-F} 23.7, C5), 91.3 (C3), 55.8 (OMe), 53.4 (OMe).

n_{max} /cm^{-1}: 1616, 1581 (s, C=N and C=C), 1207 (s, C-O).

m/z: 207 (100%, M^+), 206 (88%, M^+ - H), 176 (40%, M^+ - OMe), 120 (37%), 94 (17%, $C_6H_3F^+$).

EXAMPLE 40. 2,4-Dichloro-5,7-dimethylquinoline



$C_8H_{11}N$
Mol. Wt: 121.2

$C_{11}H_9Cl_2N$
Mol. Wt: 226.1

3,5-Dimethylaniline (5.0 g, 41 mmol), malonic acid (6.4 g, 0.62 mmol) and phosphorus oxychloride (40 ml) were heated under reflux for 5 hours. The mixture was poured into crushed ice and made alkaline with 5M NaOH, left to stand overnight, and then filtered to give the crude product as a brown solid. Soxhlet extraction with hexane gave the title compound as yellow needles. Yield 5.9 g, 64%. Melting point 79-81°C.

Found M^+: 225.0114. $C_{11}H_9{}^{35}Cl_2N$ requires 225.0112.

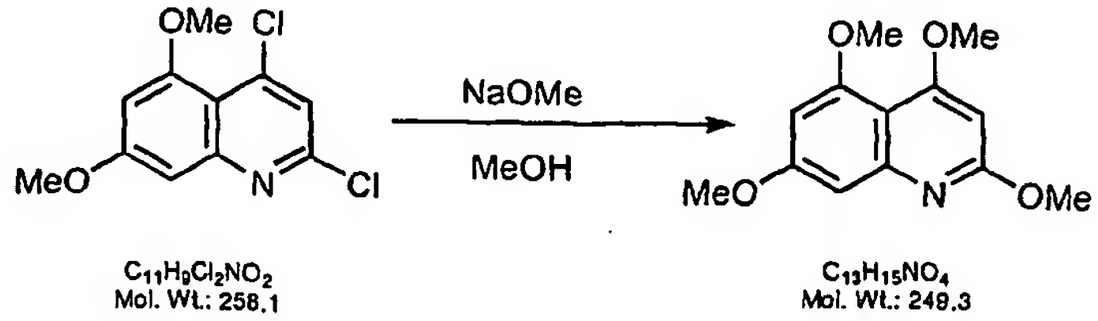
δ_H: 7.62 (1H, s, H8), 7.33 (1H, s, H6), 7.17 (1H, s, H3), 2.93 (3H, s, 5-Me), 2.46 (3H, s, 7-Me).

δ_C: 150.8 (C2), 149.4 (C4), 144.6, 141.6, 135.5 (C5, C7, C8a), 133.8, 127.6, 123.1 (C3, C6, C8), 122.9 (C4a), 25.4 (Me), 21.8 (Me).

n_{max}/cm^{-1}: 1622, 1562 (s, C=C, C=N).

m/z: 229 (11%, $M^+ \cdot {}^{37}Cl_2$), 227 (60%, $M^+ {}^{37}Cl^{35}Cl$), 225 (100%, $M^+ {}^{35}Cl_2$), 212 (28%, $M^+ {}^{37}Cl^{35}Cl$ - Me), 210 (33%, $M^+ {}^{35}Cl_2$ - Me), 190 (9%, M^+ - Cl).

EXAMPLE 41. 2,4,5,7 -Tetramethoxyquinoline



$C_{11}H_9Cl_2NO_2$
Mol. Wt: 258.1

$C_{13}H_{15}NO_4$
Mol. Wt: 249.3

2,4-Dichloro-5,7-dimethoxyquinoline (**EXAMPLE 16**) (0.16 g, 0.62 mmol) was heated under reflux in methanolic sodium methoxide (0.50 g Na in 25 ml MeOH)

for 48 hours. After cooling, the mixture was poured into water and neutralised (0.5M HCl), then left to stand for 1 hour before filtering to give the product as white needles. Yield 0.12 g, 78%. Melting point 129-131°C.

Found M^+: 249.0097. $C_{13}H_{15}NO_4$ requires 249.1001.

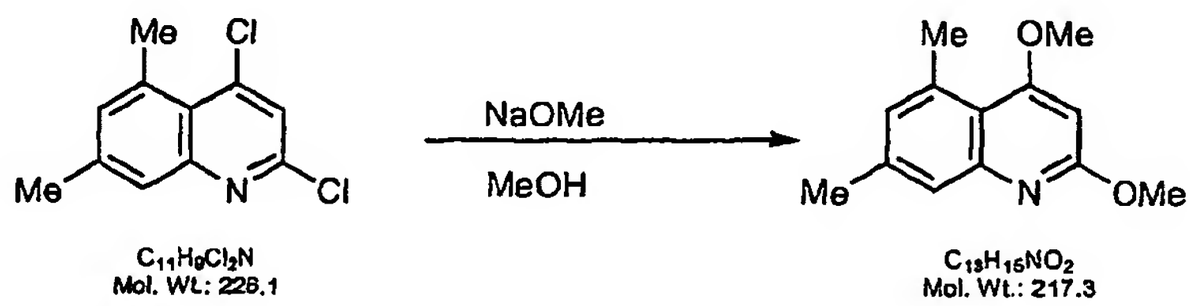
δ_H: 6.81 (1H, d, *J* 2.2, H8), 6.38 (1H, d, *J* 2.2, H6), 6.09 (1H, s, H3), 4.02 (3H, s, OMe), 3.94 (3H, s, OMe), 3.90 (6H, s, 2 x OMe).

δ_C: 166.3, 164.7, 161.6, 158.5, (C2, C4, C5, C7), 151.7, 105.8 (C4a), 100.1, 97.0, 89.3 (C6, C8, C3), 56.5, 56.3, 55.8, 53.6 (4 x OMe).

n_{max}/cm^{-1}: 1610, 1594 (s, C=N, C=C), 1210, 1063 (s, C-O-C).

m/z: 249 (100%, M^+), 248 (85%, M^+ - H), 220 (14%), 143 (16%).

EXAMPLE 42. 2,4-Dimethoxy-5,7-dimethylquinoline



$C_{11}H_9Cl_2N$
Mol. Wt: 226.1

$C_{13}H_{15}NO_2$
Mol. Wt.: 217.3

2,4-Dichloro-5,7-dimethylquinoline (**EXAMPLE 40**) (2.0 g, 8.8 mmol) was heated under reflux in methanolic sodium methoxide (2.0 g Na in 75 ml MeOH) for 48 hours. The mixture was poured into cold water, left to stand for 1 hour, and then filtered to give the title compound as white needles. Yield 1.6 g, 84%. Melting point 75-77°C.

Found M^+: 217.1091. $C_{13}H_{15}NO_2$ requires 217.1103.

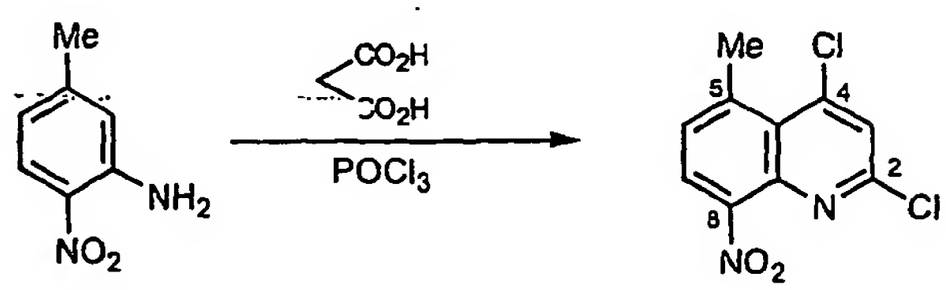
δ_H: 7.42 (1H, s, H8), 6.89 (1H, s, H6), 6.11 (1H, s, H3), 4.02 (3H, s, 2-OMe), 3.89 (3H, s, 4-OMe), 2.73 (3H, s, Me), 2.40 (3H, s, Me).

δ_C: 166.6 (C2), 163.3 (C4), 149.0, 139.3, 135.1 (C5, C7, C8a), 128.5, 125.0, 116.3 (C4a), 90.1 (C3), 55.3 (OMe), 53.2 (OMe), 24.2 (Me), 21.3 (Me).

n_{max}/cm^{-1}: 1615, 1584 (s, C=C, C=N), 1208, 1038 (s, C-O-C).

m/z: 217 (94%, M^+), 216 (100%, M^+ - H), 202 (49%, M^+ - Me), 187 (87%, M -2Me), 172 (50%, M^+ - 3Me), 115 (53%).

EXAMPLE 43. 2,4-Dichloro-5-methyl-8-nitroquinoline



$C_7H_8N_2O_2$
Mol. Wt: 152.2

$C_{10}H_6Cl_2N_2O_2$
Mol. Wt: 257.1

5-Methyl-2-nitroaniline (3.0 g, 20 *mmol*), malonic acid (3.1 g, 30 mmol) and phosphorus oxychloride (25 ml) were heated under reflux for 7 hours, and then poured into crushed ice and made alkaline (5M NaOH) before filtering to give a crude brown solid. Soxhlet extraction (hexane, 6 h) of the crude solid gave the pure product as yellow needles. Yield 1.6 g, 31%. Melting point 126-128°C. (Found C: 48.70, H: 2.76, N: 10.27%. $C_{10}H_6Cl_2N_2O_2$ requires C: 46.72, H: 2.35, N: 10.90%.)

Found M^+: 255.9804. $C_{10}H_6{}^{35}Cl_2N_2O_2$ requires 255.9806.

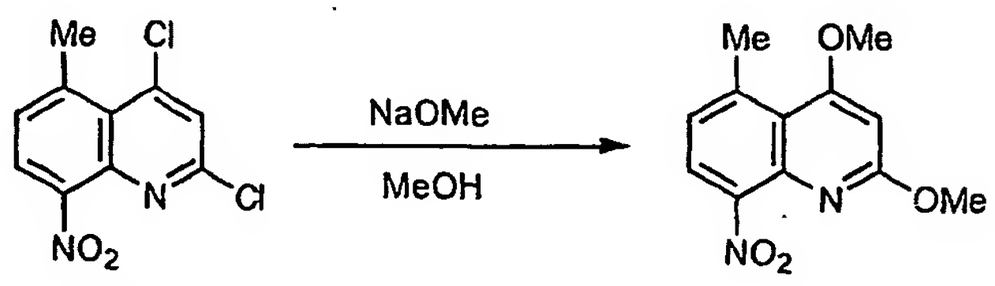
δ_H: 7.81 (1H, d, *J* 8.0, H7), 7.60 (1H, s, H3), 7.45 (1H, d, *J* 8.0, H6), 3.08 (3H, s, 5-Me).

δ_C: 152.0, 147.4, 145.3, 141.6, 141.1 (C2, C4, C8, C8a, C5), 130.0, 126.2 (C6, C7), 125.5 (C4a), 124.6 (C3), 26.1 (5-Me).

n_{max} /cm^{-1}: 1609, 1567 (m, C=C, C=N), 1528 (s, N=O), 874 (m, C-N).

m/z: 260 (12%, $M^+ {}^{37}Cl_2$), 258 (55%, $M^+ {}^{37}Cl{}^{35}Cl$), 256 (100%, $M^+ {}^{35}Cl_2$), 228 (21%), 226 (29%, M^+ - NO).

EXAMPLE 44. 2,4-Dimethoxy-5-methyl-8-nitroquinoline



$C_{10}H_6Cl_2N_2O_2$
Mol. Wt: 257.1

$C_{12}H_{12}N_2O_4$
Mol. Wt: 248.2

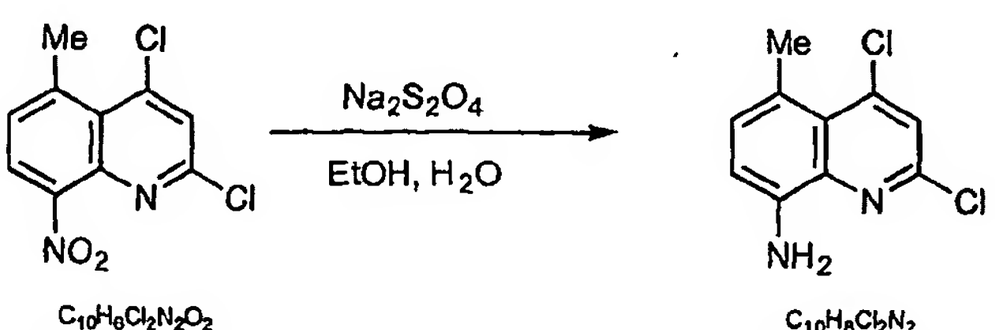
2,4-Dichloro-5-methyl-8-nitroquinoline (**EXAMPLE 43**) (1.0 g, 3.9 mmol) was heated under reflux in excess methanolic sodium methoxide (1.0 g Na in 50 ml MeOH) for 48 hours. The mixture was then cooled, poured into water and filtered to give the product as a brown powder. Yield 0.4 g, 41%. Melting point >250°C. Found M^+: 248.0815. $C_{12}H_{12}N_2O_4$ requires 248.0797.

δ_H: 7.73 (1H, d, *J* 7.9, H7), 7.09 (1H, d, *J* 7.9, H6), 6.27 (1H, s, H3), 4.01 (3H, s, OMe), 3.96 (3H, s, OMe), 2.82 (3H, s, 5-Me).

n_{max} /cm^{-1}: 1606 (s, C=C or C=N), 1523 (s, N=O), 1208 (s, C-O).

m/z: 248 (31%, M^+), 247 (20%, M^+ - H), 218 (18%), 204 (16%), 143 (49%), 100 (100%).

EXAMPLE 45. 8-Amino-2,4-dichloro-5-methylquinoline



$C_{10}H_6Cl_2N_2O_2$
Mol. Wt: 257.1

$C_{10}H_8Cl_2N_2$
Mol. Wt: 227.1

2,4-Dichloro-5-methyl-8-nitroquinoline (**EXAMPLE 43**) (0.30 g, 1.2 mmol) and sodium dithionite (1 g, 5.8 mmol) were heated under reflux in 50% aqueous ethanol (50 ml) for 4 hours. The mixture was made alkaline with 1M NaOH, and then extracted with ether (3 x 30 ml). The combined organic extracts were dried

over magnesium sulfate, and then the solvent evaporated under reduced pressure to give the product as a yellow powder. Yield 0.22 g, 83%. Melting point 116-118°C.

Found M^+: 226.0244. $C_{10}H_8{}^{35}Cl_2N_2$ requires 226.0065.

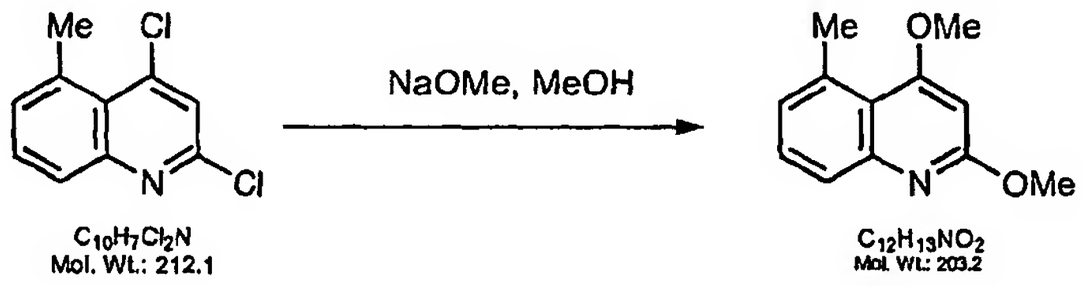
δ_H: 7.41 (1H, s, H3), 7.14 (1H, dd, *J* 7.9, 0.5, H6), 6.86 (1H, d, *J* 7.9, H7), 4.84 (2H, br s, NH_2), 2.85 (3H, d, *J* 0.5, 5-Me).

δ_C: 146.4, 144.7, 142.2, 139.9 (C2, C4, C8, C8a), 131.8, 125.0 (C5), 123.8, 122.9 (C4a), 111.8 (C3), 24.4 (5-Me).

n_{max} /cm^{-1}: 3422, 3322 (w, N-H), 1610, 1554 (s, C=C, C=N).

m/z: 230 (11%, M^+ $^{37}Cl_2$), 228 (67%, M^+ $^{37}Cl^{35}Cl$), 226 (100%, M^+ $^{35}Cl_2$), 225 (49%, M^+ - H).

EXAMPLE 46. 2,4-Dimethoxy-5-methylquinoline



$C_{10}H_7Cl_2N$
Mol. Wt.: 212.1

$C_{12}H_{13}NO_2$
Mol. Wt.: 203.2

2,4-Dichloro-5-methylquinoline (**EXAMPLE 17**) (0.12 g, 0.57 mmol) was heated under reflux in methanolic sodium methoxide (0.50 g Na in 40 ml MeOH) for 40 hours. After cooling the mixture was poured into ice-cold water, and left to stand for 1 hour before filtering under reduced pressure to give the product as off-white needles. Yield 85 mg, 73%. Melting point 58-60°C.

Found M^+: 203.0953. $C_{12}H_{13}NO_2$ requires 203.0946.

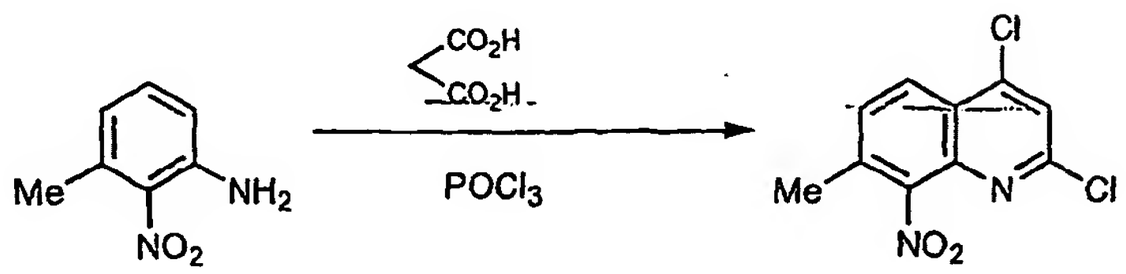
δ_H: 7.62 (1H, d, *J* 8.3, H5), 7.42 (1H, dd, *J* 8.3, 7.2, H7), 7.07 (1H, d, *J* 7.2, H6), 6.19 (1H, s, H3), 4.04 (3H, s, OMe), 3.93 (3H, s, OMe), 2.79 (3H, s, 5-Me).

δ_C: 166.6, 163.1 (C2, C4), 148.8, 135.5 (C8a, C5), 129.2, 126.4, 125.5 (C6, C7, C8), 118.6 (C4a), 90.8 (C3), 55.3 (OMe), 53.2 (OMe), 24.3 (5-Me).

n_{max} /cm^{-1}: 1611, 1588 (s, C=C, C=N), 1207 (s, C-O).

m/z: 203 (100%, M^+), 202 (49%, M^+ - H), 173 (15%).

EXAMPLE 47. 2,4-Dichloro-7-methyl-8-nitroquinoline



$C_7H_8N_2O_2$
Mol. Wt: 152.2

$C_{10}H_6Cl_2N_2O_2$
Mol. Wt: 257.1

3-Methyl-2-nitroaniline (**EXAMPLE 2**) (4.0 g, 26 mmol) and malonic acid (4.1 g, 39 mmol) were heated in phosphorus oxychloride (40 ml) for 6 hours. Standard workup and Soxhlet extraction (hexane, 4h) yielded the title compound as yellow needles. Yield 0.90 g 13%. Melting point 108-110°C.

Found M^+: 255.9797. $C_{10}H_6{}^{35}Cl_2N_2O_2$ requires 255.9806.

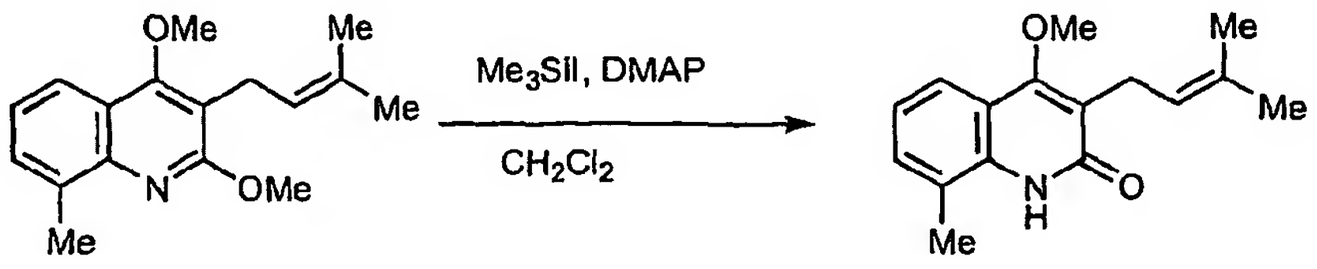
δ_H: 8.20 (1H, d, *J* 8.6, H5), 7.57 (1H, s, H3), 7.55 (1H, d, *J* 8.6, H6), 2.55 (3H, s, Me).

δ_C: 152.3, 144.3, 139.6, 132.9 (C2, C4, C8, C8a), 130.2 (CH), 126.3, 125.6 (CH), 124.0, 123.3 (CH), 17.6 (Me)

n_{max}/cm^{-1}: 1623, 1574 (s, C=C, C=N), 1537 (s, N=O).

m/z: 258 (48%, M^+ $^{37}Cl^{35}Cl$), 256 (73%, M^+ $^{35}Cl_2$), 174 (100%), 139 (56%).

EXAMPLE 48. 4-Methoxy-8-methyl-3-(3-methylbut-2-enyl)-1*H*-quinolin-2-one



$C_{17}H_{21}NO_2$
Mol. Wt.: 271.4

$C_{16}H_{19}NO_2$
Mol. Wt.: 257.3

2,4-Dimethoxy-8-methyl-3-(3-methyl-2-butenyl)quinoline (**EXAMPLE 23**) (0.40 g, 1.5 mmol) and 4-dimethylaminopyridine (0.18 g, 1.5 mmol) were dissolved in dry dichloromethane (20 ml) and cooled to -78°C. Iodotrimethylsilane (0.30 g, 1.5 mmol) was added dropwise, and the mixture allowed to attain room temperature over a period of 1 hour, and then stirred for a further 40 hours at room temperature. The mixture was then poured into water, washed with 0.1M hydrochloric acid (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to give a brown residue. Column chromatography (1:1 hexane:EtOAc) furnished the pure quinoline (R_f 0.31) as a pale yellow solid. Yield 0.2g, 55%.

Melting point 135-138°C.

Found M^+: 257.1426. $C_{16}H_{19}NO_2$ requires 257.1416.

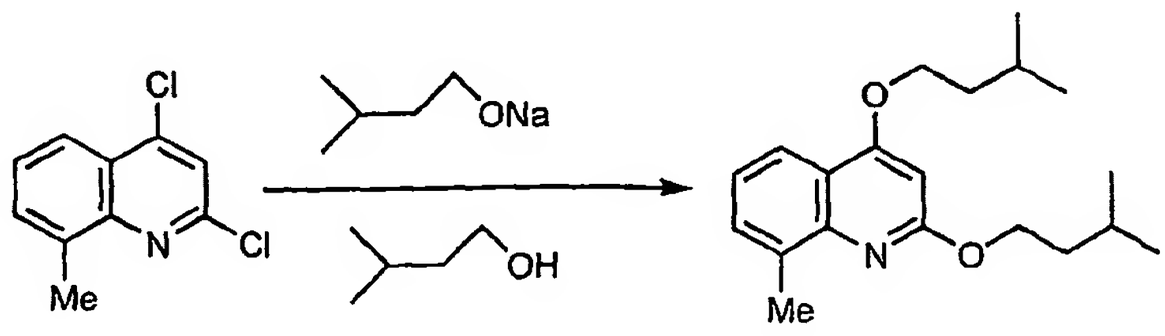
δ_H: 10.20 (1H, br s, NH), 7.63 (1H, d, *J* 8.0, H5), 7.29 (1H, d, *J* 7.3, H7), 7.11 (1H, dd, *J* 8.0, 7.3, H6), 5.29 (1H, t, *J* 6.9, $Me_2C=C\underline{H}$), 3.92 (3H, s, OMe), 3.40 (2H, d, *J* 6.9, $C\underline{H}_2CH=CMe_2$), 2.52 (3H, s, 8-Me), 1.81 (3H, s, $C=CC\underline{H}_3$), 1.69 (3H, s, $C=CC\underline{H}_3$).

δ_C: 164.8, 162.4 (C2, C4), 135.8, 132.5 (C8, C8a), 131.2 (CH), 123.3, 122.2 (C4a and $=\underline{C}Me_2$), 121.9 (CH), 121.5 (CH), 121.0 (CH), 117.1 (C3), 61.8 (OMe), 25.7 (Me), 23.5 (CH_2), 18.0 (Me), 17.1 (Me).

n_{max}/cm^{-1}: 3400 (w, NH), 1636 (s, C=O).

m/z: 257 (66%, M^+), 242 (92%, M^+ - Me), 214 (100%, M^+ - CMe_2), 188 (54%, M^+ - $Me_2C=CHCH_2$).

EXAMPLE 49. 2,4-Diisopentyloxy-8-methylquinoline



$C_{10}H_7Cl_2N$
Mol. Wt.: 212.1

$C_{20}H_{29}NO_2$
Mol. Wt.: 315.5

2,4-Dichloro-8-methylquinoline (**EXAMPLE 9**) (0.50 g, 2.4 mmol) was heated at 90°C in excess sodium isopentyloxide/isopentyl alcohol (1.0 g Na in 50 ml isopentyl alcohol) for 48 hours. The mixture was then cooled, neutralised with 2M HCl, and extracted with ether (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated to yield the pure product as a colourless oil. Yield 0.31 g, 41%.

Found M^+: 315.2199. $C_{20}H_{29}NO_2$ requires 315.2198.

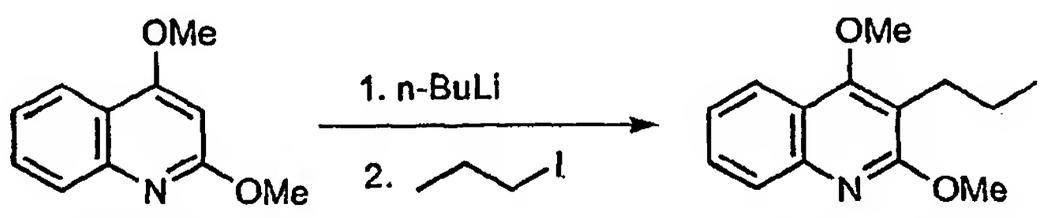
δ_H: 7.91 (1H, d, *J* 7.5, H5), 7.43 (1H, d, *J* 7.0, H7), 7.19 (1H, dd, *J* 7.5, 7.0, H6), 6.19 (1H, s, H3), 4.52 (2H, t, *J* 6.8, $OC\underline{H}_2$), 4.11 (2H, t, *J* 6.5, $OC\underline{H}_2$), 2.66 (3H, s, 8-Me), 1.95-1.70 (6H, m, 2 x $C\underline{H}Me_2$ and 2 x $OCH_2C\underline{H}_2$), 1.00-0.98 (12H, m, 2 x $CH(C\underline{H}_3)_2$).

δ_C: 163.9, 162.9 (C2, C4), 146.3 (C8a), 135.2 (C8), 130.4, 122.9, 120.0 (C5, C6, C7), 119.4 (C4a), 91.3 (C3), 67.2($O\underline{C}H_2$), 64.5 ($O\underline{C}H_2$), 38.4 ($OCH_2\underline{C}H_2$), 38.0 ($OCH_2\underline{C}H_2$), 25.7 (8-Me), 23.2, 23.0, 18.5.

n_{max} / cm^{-1}: 1612, 1601 (s, C=C, C=N).

m/z: 315 (32%, M^+), 245 (49%), 175 (100%, $C_{10}H_9NO_2^+$).

EXAMPLE 50. 2,4-Dimethoxy-3-propylquinoline



$C_{11}H_{11}NO_2$
Mol. Wt: 189.2

$C_{14}H_{17}NO_2$
Mol. Wt: 231.3

A solution of 2,4-dimethoxyquinoline (**EXAMPLE 4A**) (0.30 g, 1.6 mmol) in THF (15 ml) was cooled to 0°C under argon, *n*-butyllithium (0.80 ml of 2.5M solution in hexane) was added, and the mixture stirred for 1 hour at 0°C. 1-Iodopropane (0.34 g, 2 mmol) was added dropwise, the mixture was stirred at 0°C for 30 minutes and then was allowed to warm to room temperature overnight. The reaction mixture was poured into water and extracted with ether (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to

give a yellow oil, which was purified by column chromatography (9:1 hexane:EtOAc) to give the title compound as a colourless oil, R_f 0.67 (9:1 hexane:EtOAc). Yield 65 mg, 17% (approximately 150 mg of starting material also recovered).

Found M^+: 231.1267. $C_{14}H_{17}NO_2$ requires 231.1259.

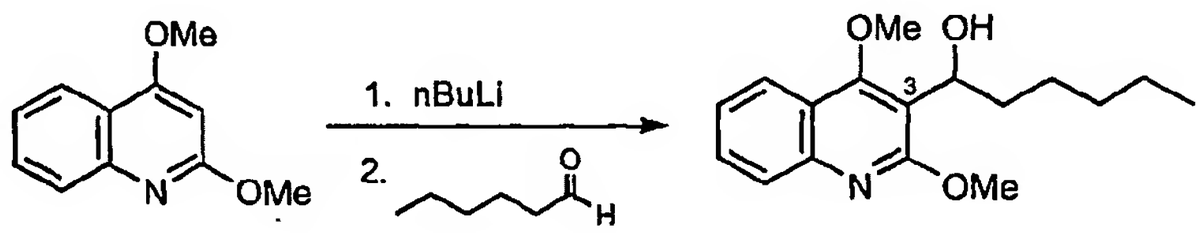
δ_H: 7.90 (1H, dd, *J* 8.2, 1.4, H5), 7.82 (1H, br. d, *J* 8.2, H8), 7.55 (1H, ddd, *J* 8.2, 6.9, 1.4, H7), 7.35 (1H, ddd, *J* 8.2, 6.9, 1.0, H6), 2.70 (2H, t, *J* 7.7, $C\underline{H_2}CH_2CH_3$), 1.63 (2H, m, $CH_2C\underline{H_2}CH_3$), 1.00 (3H, t, *J* 7.4, $CH_2CH_2C\underline{H_3}$)

δ_C: 162.7, 161.7 (C2, C4), 146.1 (C8a), 128.8, 127.3, 123.6, 122.0 (C5, C6, C7, C8), 121.1, 118.0 (C4a and C3), 62.3 (OMe), 53.7 (OMe), 26.2 ($\underline{C1'}H_2$), 22.7 ($\underline{C2'}H_2$), 14.4 ($\underline{C3'}H_3$).

n_{max} /cm^{-1}: 3064, 2956, 2871 (m, C-H), 1620, 1573 (s, C=C, C=N), 1086, 1012 (s, C-O-C)

m/z: 231 (53%, M^+), 216 (38%, M^+ - Me), 202 (61%, M^+ - CH_3CH_2).

EXAMPLE 51. 2,4-Dimethoxy-3-(1'-hydroxy-n-hexyl)quinoline



$C_{11}H_{11}NO_2$
Mol. Wt: 189.2

$C_{17}H_{23}NO_3$
Mol. Wt: 289.4

2,4-Dimethoxyquinoline (**EXAMPLE 4A**) (0.30 g, 1.6 mmol) in THF (20 ml) was cooled to 0°C, and *n*-butyllithium (0.80 ml of a 2.5M solution in hexanes) was added with stirring. Stirring was continued at 0°C for 45 minutes. Hexanal (0.24 g, 2.4 mmol) was added and the mixture stirred at 0°C for 15 minutes, then allowed to warm to room temperature for 45 minutes. The flask contents were poured into water, and the mixture extracted with diethyl ether (3 x 30 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to give

a dark yellow oil. Column chromatography (2:1 hexane:EtOAc) furnished the pure product as a pale yellow oil. Yield 0.21g, 45%.

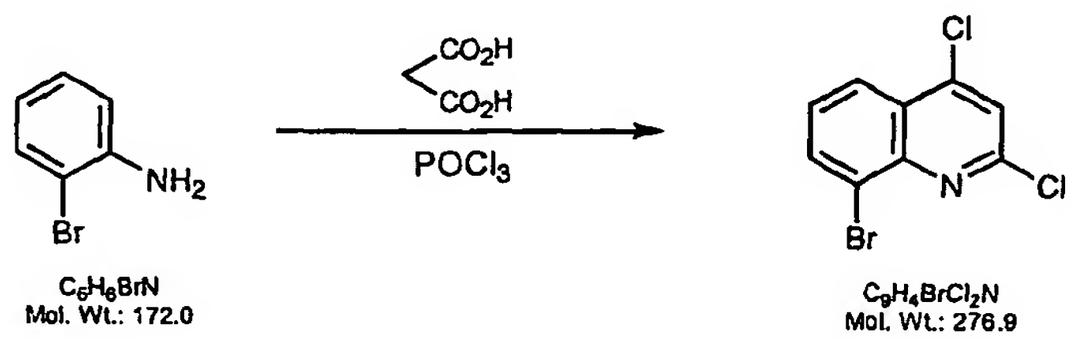
Found M^+: 289.1670. $C_{17}H_{23}NO_3$ requires 289.1678.

δ_H: 7.93 (1H, dd, *J* 8.1, 1.3, H5), 7.83 (1H, dd, *J* 8.4, 1.0, H8), 7.60 (1H, ddd, *J* 8.4, 7.0, 1.3, H7), 7.40 (1H, ddd, *J* 8.1, 7.0, 1.0, H6), 5.11 (1H, m, $C\underline{H}OH$), 4.13 (3H, s, OMe), 4.00 (3H, s, OMe), 3.38 (1H, d, *J* 11.5, OH), 2.01 (1H, m, $ArCH(OH)C\underline{H_a}H_b$), 1.77 (1H, m, $ArCH(OH)CH_a\underline{H_b}$), 1.39-1.25 (6H, m), 0.90 (3H, m, $ArCH(OH)(CH_2)_4\underline{CH_3}$).

n_{max}/cm^{-1}: 3995 (m br, OH), 1644, 1602, 1574 (s, C=C, C=N).

m/z: 289 (12%, M^+), 218 (100%, $M^+ - CH_3(CH_2)_4$).

EXAMPLE 52. 8-Bromo-2,4-dichloroquinoline



C_6H_6BrN
Mol. Wt.: 172.0

$C_9H_4BrCl_2N$
Mol. Wt.: 276.9

2-Bromoaniline (2.0 g, 12 mmol), malonic acid (1.9 g, 18 mmol) and phosphorus oxychloride (30 ml) were heated under reflux for 6 hours. After alkaline aqueous workup and filtration, the crude solid product was continuously extracted with hexane for 6 hours to give the pure quinoline as a pale yellow powder. Yield 1.0g, 31%.

Melting point 101-103°C.

Found M^+: 276.8884 (^{81}Br), 274.8898 (^{79}Br). $C_9H_4Br^{35}Cl_2N$ requires 276.8885 and 274.8905.

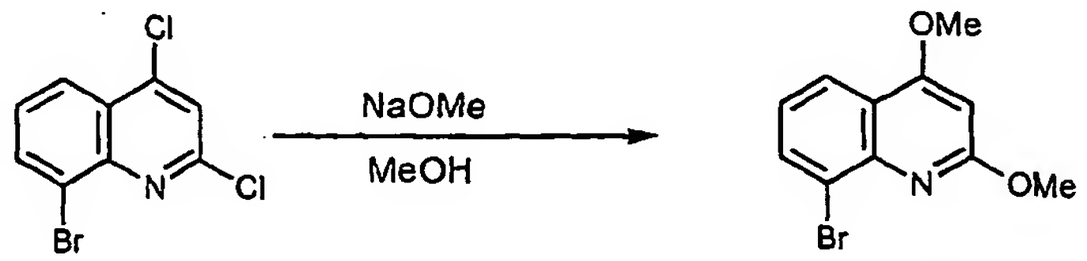
δ_H: 8.17 (1H, dd, *J* 8.3, 1.3, H5), 8.11 (1H, dd, *J* 7.6, 1.3, H7), 7.57 (1H, s, H3), 7.50 (1H, dd, *J* 8.3, 7.6, H6).

δ_C: 150.9, 145.5, 144.7, (C2, C4, C8a), 135.3, 128.2, 126.5 (C4a), 124.1, 123.0 (one quaternary C missing).

n_{max} /cm^{-1}: 1573 (s, C=N).

m/z: 279 (41%, M$^+$ $^{79}Br^{37}Cl_2$ and M$^+$ $^{81}Br^{37}Cl^{35}Cl$), 277 (100%, M$^+$ $^{81}Br^{35}Cl_2$ and M$^+$, $^{79}Br^{37}Cl^{35}Cl$), 275 (60%, M$^+$, $^{79}Br^{35}Cl_2$), 242 (26%, M$^+$ (277) - ^{35}Cl), 161 (17%, M$^+$ - Br, Cl).

EXAMPLE 53. 8-Bromo-2,4-dimethoxyquinoline



$C_9H_4BrCl_2N$
Mol. Wt.: 276.9

$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

8-Bromo-2,4-dichloroquinoline (**EXAMPLE 52**) (0.80 g, 2.9 mmol) was heated under reflux in excess methanolic sodium methoxide (1.0 g Na in 50 ml MeOH). After aqueous workup and filtration the product was isolated as white needles. Yield 0.50 g, 64%. Melting point 120-123°C. (Found C: 49.07, H: 3.55, N: 5.10%. $C_{11}H_{10}BrNO_2$ requires C: 49.28, H: 3.76, N: 5.10%.)

Found M$^+$: 266.9872. $C_{11}H_{10}{}^{79}BrNO_2$ requires 266.9894.

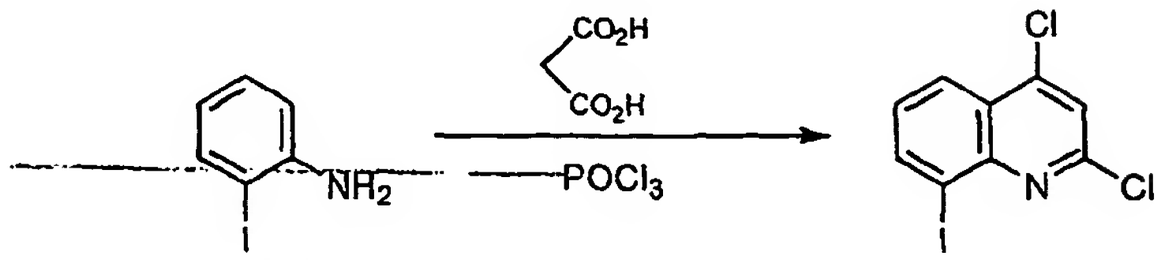
δ_H: 8.03 (1H, dd, *J* 8.2, 1.4, H5), 7.93 (1H, dd, *J* 7.5, 1.4, H7), 7.18 (1H, dd, *J* 8.2, 7.5, H6), 6.27 (1H, s, H3), 4.13 (3H, s, OMe), 4.00 (3H, s, OMe).

δ_C: 164.1, 144.2, 133.7 (CH), 123.6 (CH), 122.3, 121.6 (CH), 120.5, 91.2 (C3), 56.1 (OMe), 53.8 (OMe) (one quaternary C missing).

n_{max} / cm^{-1}: 1620, 1600, 1565 (s, C=C and C=N).

m/z: 269 (100%, M$^+$ ^{81}Br), 268 (92%, M$^+$ ^{81}Br - H), 267 (96%, M$^+$ ^{79}Br), 266 (81%, M$^+$ ^{79}Br - H), 243 (42%), 189 (40%), 188 (45%, M$^+$ - Br).

EXAMPLE 54. 2,4-Dichloro-8-iodoquinoline



C6H6IN
Mol. Wt: 219.0

C9H4Cl2IN
Mol. Wt: 323.9

2-Iodoaniline (7.0 g, 32 mmol) and malonic acid (5.0 g, 48 mmol) were heated under reflux in phosphorus oxychloride (40 ml) for 5 hours. After standard workup and Soxhlet extraction of the crude with hexane, the pure product was obtained as bright yellow needles, yield 1.3 g, 12.5%. R_f (9:1 hexane:EtOAc) 0.65. Melting point 80-82°C.

Found M^+: 322.8764. $C_9H_4{}^{35}Cl_2IN$ requires 322.8767.

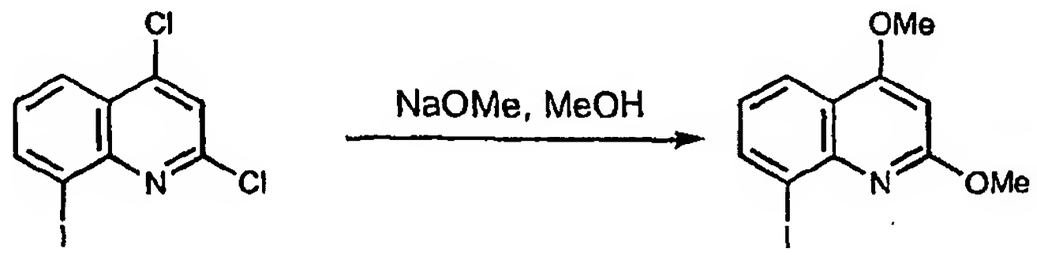
δ_H: 8.37 (1H, dd, *J* 7.5, 0.9, H7), 8.16 (1H, dd, *J* 8.4, 0.9, H5), 7.54 (1H, s, H3), 7.34 (1H, dd, *J* 8.4, 7.5, H6).

δ_C: 149.8 (C2), 146.2 (C8a), 143.5 (C4), 141.1 (C7), 127.8, 124.5 (C4a), 123.9, 121.8 (C3), 100.8 (C8).

n_{max} / cm^{-1}: 1595, 1575 (s, C=C, C=N), 1271 (s).

m/z: 327 (13%, $M^+ {}^{37}Cl_2$), 325 (74%, $M^+ {}^{37}Cl\,{}^{35}Cl$), 323 (100%, $M^+ {}^{35}Cl_2$), 196 (25%, M^+ (323) - I), 161 (29%, M^+ - I, Cl).

EXAMPLE 55. 2,4-Dimethoxy-8-iodoquinoline



C9H4Cl2IN
Mol. Wt: 323.9

C11H10INO2
Mol. Wt: 315.1

2,4-Dichloro-8-iodoquinoline (**EXAMPLE 54**) (1.0 g, 3 mmol) was heated under reflux in methanolic sodium methoxide (1.0 g Na in 50 ml MeOH) for 40 hours. After aqueous workup and filtration the title compound was obtained as pale yellow needles. Yield 0.81 g, 86%.

Melting point: 105-107°C. (Found C: 41.47, H: 3.19, N: 3.91%. $C_{11}H_{10}INO_2$ requires C: 41.93, H: 3.20, N: 4.45%.)

Found M^+: 314.9756. $C_{11}H_{10}INO_2$ requires 314.9758.

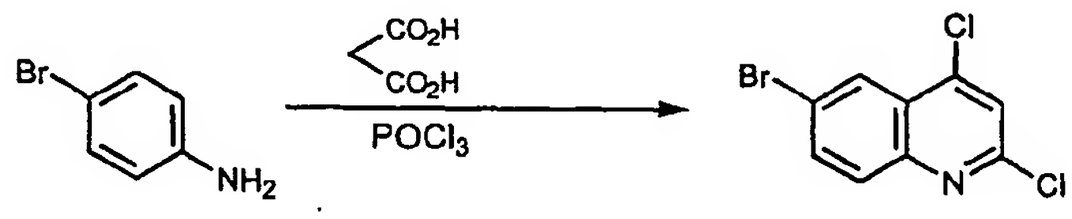
δ_H: 8.18 (1H, dd, *J* 7.4, 1.4, H7), 8.04 (1H, dd, *J* 8.1, 1.4, H5), 7.05 (1H, dd, *J* 8.1, 7.4, H6), 6.24 (1H, s, H3), 4.13 (3H, s, OMe), 3.99 (3H, s, OMe).

δ_C: 164.2, 164.1 (C2 and C4), 146.1 (C8a), 140.3 (C7), 124.5, 122.5 (C5 and C6), 119.5 (C4a), 100.4 (C8), 91.0 (C3), 56.1 (OMe), 54.0 (OMe).

n_{max} / cm^{-1}: 1619, 1562 (s, C=C, C=N), 1213 (s, C-O).

m/z: 315 (100%, M^+), 314 (26%, M^+ - H), 285 (12%).

EXAMPLE 56. 6-Bromo-2,4-dichloroquinoline



C_8H_8BrN
Mol. Wt.: 172.0

$C_9H_4BrCl_2N$
Mol. Wt.: 276.9

4-Bromoaniline (7.0 g, 41 mmol), malonic acid (6.3 g, 61 mmol) and phosphorus oxychloride (50 ml) were heated under reflux for 6 hours. After standard workup and Soxhlet extraction with hexane the product was obtained as yellow needles. Yield 3.2 g, 28%. Melting point 132-134°C.

Found M^+: 274.8897. $C_9H_4{}^{79}Br{}^{35}Cl_2N$ requires 274.8905.

δ_H: 8.31 (1H, d, *J* 1.3, H5), 7.88-7.82 (2H, m, H7 and H8), 7.50 (1H, s, H3)

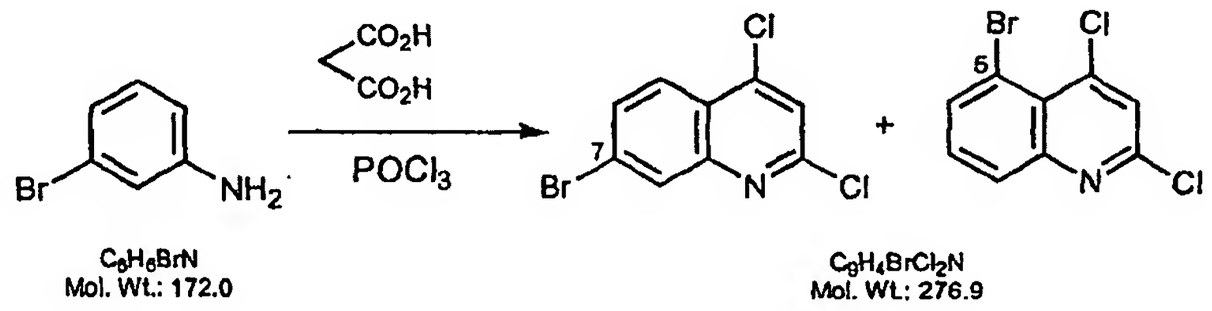
δ_C: 150.7 (C2), 147.1 (C4), 143.6 (C8a), 135.5, 131.0, 126.9 (all Ar-H), 126.6, 123.2, 126.4.

n_{max}/cm^{-1}: 1570, 1547 (s, C=N, C=C).

m/z: 281 (5%, M^+ $^{81}Br^{37}Cl_2$), 279 (49%, M^+ $^{79}Br^{37}Cl_2$ and M^+ $^{81}Br^{37}Cl^{35}Cl$), 277 (100%, M^+ $^{81}Br^{35}Cl_2$ and M^+ $^{79}Br^{37}Cl^{35}Cl$), 275 (62%, M^+ $^{79}Br^{35}Cl_2$), 242 (21%, M^+ - Cl), 161 (20%).

EXAMPLE 57A. 5-Bromo-2,4-dichloroquinoline and

EXAMPLE 57B. 7-bromo-2,4-dichloroquinoline



C_9H_6BrN
Mol. Wt.: 172.0

$C_9H_4BrCl_2N$
Mol. Wt.: 276.9

3-Bromoaniline (7.0 g, 41 mmol) and malonic acid (6.4 g, 62 mmol) were heated under reflux in phosphorus oxychloride (40 ml) for 6 hours. Standard workup gave the crude product as a brown powder. Soxhlet extraction with hexane yielded a mixture of the two isomeric products; R_f 0.58 and 0.42 (95:5 hexane:EtOAc).

Column chromatography furnished the two products as white needles.

Data for 5-bromo-2,4-dichloroquinoline (EXAMPLE 57A)

Yield 0.70g , 6%. Melting point 130-132°C. R_f 0.42 (95:5 hexane:EtOAc).

Found M^+: 274.8908. $C_9H_4{}^{79}Br^{35}Cl_2N$ requires 274.8905.

δ_H: 7.99 (1H, dd, *J* 8.4, 1.2, H8), 7.93 (1H, dd, *J* 7.5, 1.2, H6), 7.55 (1H, s, H3), 7.53 (1H, dd, *J* 8.4, 7.5, H7).

δ_C: 150.2 (C2), 149.9 (C4), 144.3 (C8a), 135.6, 131.1, 130.0, 125.3, 123.4, 117.7.

n_{max}/cm^{-1}: 1564, 1545 (s, C=C, C=N).

m/z: 281 (6%, M^+ $^{81}Br^{37}Cl_2$), 279 (55%, M^+ $^{79}Br^{37}Cl_2$ and M^+ $^{81}Br^{37}Cl^{35}Cl$), 277 (100%, M^+ $^{81}Br^{35}Cl_2$ and M^+ $^{79}Br^{37}Cl^{35}Cl$), 275 (75%, M^+ $^{79}Br^{35}Cl_2$), 242 (22%, M^+ - Cl), 240 (16%, M^+ $^{79}Br^{35}Cl_2$ - Cl), 196 (20%, M^+ - Br), 161 (31%, M^+ - Br, Cl).

Data for 7-bromo-2,4-dichloroquinoline (EXAMPLE 57B)

Yield 1.2 g, 11%. Melting point 102-104°C. R_f 0.58 (95:5 hexane:EtOAc). (Found C: 39.07, H: 1.12, N: 4.81%. $C_9H_4BrCl_2N$ requires C: 39.03, H: 1.46, N: 5.06%)

Found M^+: 274.8891. $C_9H_4{}^{79}Br^{35}Cl_2N$ requires 274.8905.

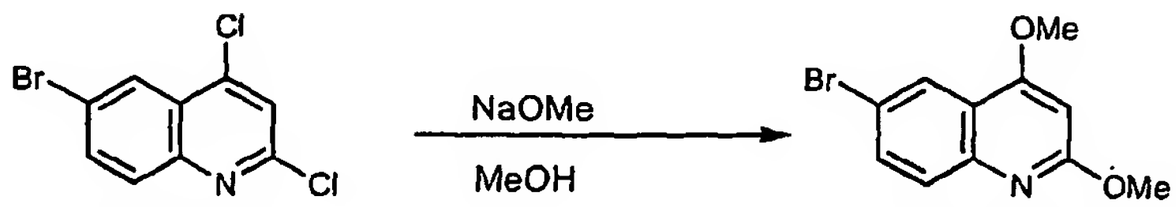
δ_H: 8.19 (1H, d, *J* 1.8, H8), 8.03 (1H, d, *J* 8.9, H5), 7.72 (1H, dd, *J*8.9, 1.8, H6), 7.50 (1H, s, H3).

δ_C: 151.1, 148.6 (C2, C4), 144.5 (C8a), 131.5 (CH), 131.3 (CH), 126.2, 125.5 (CH), 124.0, 122.4 (CH).

n_{max}/cm^{-1}: 1599, 1570, 1547 (s, C=C, C=N).

m/z: 281 (4%, $M^+ {}^{81}Br^{37}Cl_2$), 279 (45%, $M^+ {}^{79}Br^{37}Cl_2$ and $M^+ {}^{81}Br^{37}Cl^{35}Cl$), 277 (100%, $M^+ {}^{81}Br^{35}Cl_2$ and $M^+ {}^{79}Br^{37}Cl^{35}Cl$), 275 (75%, $M^+ {}^{79}Br^{35}Cl_2$), 242 (23%, M^+ - Cl), 240 (21%, $M^+ {}^{79}Br^{35}Cl_2$ - Cl), 212 (13%), 161 (20%, M^+ - Br, Cl).

EXAMPLE 58. 6-Bromo-2,4-dimethoxyquinoline



$C_9H_4BrCl_2N$
Mol. Wt: 276.9

$C_{11}H_{10}BrNO_2$
Mol. Wt: 268.1

6-Bromo-2,4-dichloroquinoline (**EXAMPLE 56**) (1.5 g, 5.4 mmol) was heated under reflux in excess methanolic sodium methoxide (1.5 g Na in 75 ml MeOH) for 48 hours, then cooled and poured into cold water. After standing for 2 hours the mixture was filtered to give the product, fine pale yellow needles. Yield 1.35 g, 93%. Melting point: 54-56°C.

Found M^+: 266.9883. $C_{11}H_{10}{}^{79}BrNO_2$ requires 266.9895.

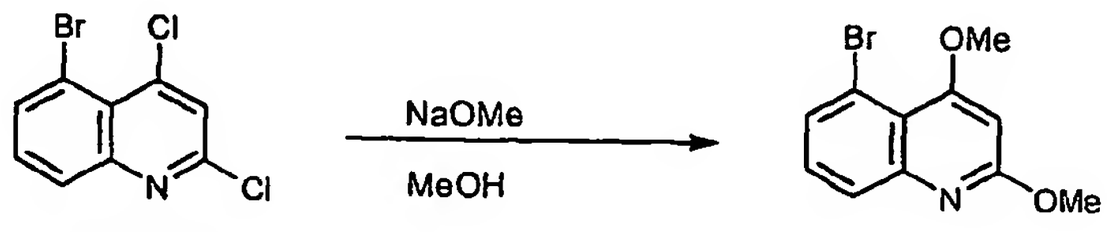
δ_H: 8.17 (1H, d, *J* 1.3, H5), 7.66-7.61 (2H, m, H7, H8), 6.20 (1H, s, H3), 4.03 (3H, s, 2-OMe), 3.96 (3H, s, 4-OMe).

δ_C: 164.5 (C2), 163.3 (C4), 146.1 (C8a), 133.5, 129.1, 124.8 (C5, C7, C8), 120.92, 117.0 (C4a, C6), 91.8 (C3), 56.2 (OMe), 53.9 (OMe).

n_{max}/cm^{-1}: 1621, 1596, 1573 (s, C=C, C=N), 1209, 1044 (s, C-O-C).

m/z: 269 (100%, M^+, ^{81}Br), 268 (95%, M^+ - H), 267 (100%, M^+, ^{79}Br), 266 (87%, M^+ - H), 239 (24%), 238 (20%), 213 (17%), 143 (22%).

EXAMPLE 59. 5-Bromo-2,4-dimethoxyquinoline



$C_9H_4BrCl_2N$
Mol. Wt: 276.9

$C_{11}H_{10}BrNO_2$
Mol. Wt: 268.1

5-Bromo-2,4-dichloroquinoline (**EXAMPLE 57A**) (0.25 g, 0.9 mmol) was heated under reflux in excess methanolic sodium methoxide (1.0 g Na in 50 ml MeOH) for 45 hours. After cooling, the mixture was poured into cold water and left to stand overnight in a refrigerator. Filtration gave the title compound as fine white needles. Yield 0.20 g, 82%. Melting point 86-88°C.

Found M^+: 266.9905. $C_{11}H_{10}{}^{79}BrNO_2$ requires 266.9895.

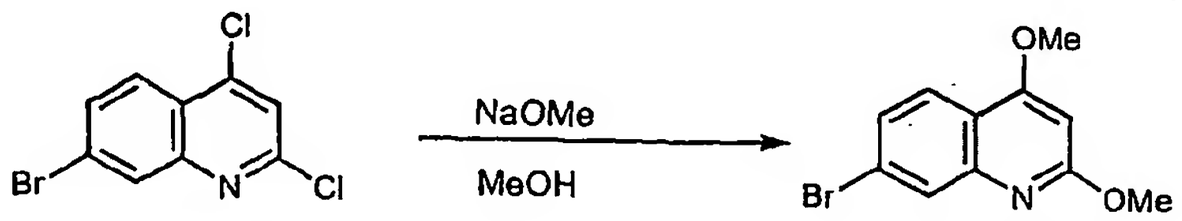
δ_H: 7.73 (1H, dd, *J* 8.1, 0.9, H8), 7.60 (1H, dd, *J* 7.6, 0.9, H6), 7.33 (1H, dd, *J* 8.1, 7.6, H7), 6.26 (1H, s, H3), 4.03 (3H, s, OMe), 3.95 (3H, s, OMe).

δ_C: 164.6, 163.8 (C2, C4), 149.9 (C8a), 131.1, 130.1, 127.7, (C6,7,8), 118.4, 116.6 (C5, C4a), 92.3 (C3), 55.8 (OMe), 53.8 (OMe).

n_{max}/cm^{-1}: 1608, 1573 (s, C=C, C=N), 1212 (s, C-O-C).

m/z: 268 (100%, M^+ ^{81}Br - H), 267 (15%, M^+ ^{79}Br), 266 (98%, M^+ ^{79}Br - H), 182 (12%), 114 (26%).

EXAMPLE 60. 7-Bromo-2,4-dimethoxyquinoline



$C_9H_4BrCl_2N$
Mol. Wt: 276.9

$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

7-Bromo-2,4-dichloroquinoline (**EXAMPLE 57B**) (0.30 g, 1.1 mmol) was heated under reflux in methanolic sodium methoxide (1.0 g Na in 50 ml MeOH) for 48 hours. After cooling, the mixture was poured into cold water, left to stand for 2 hours, and then filtered to give the title compound as white needles. Yield 0.22 g, 76%. Melting point 76-78°C.

Found M^+: 266.9871. $C_{11}H_{10}{}^{79}BrNO_2$ requires 266.9895.

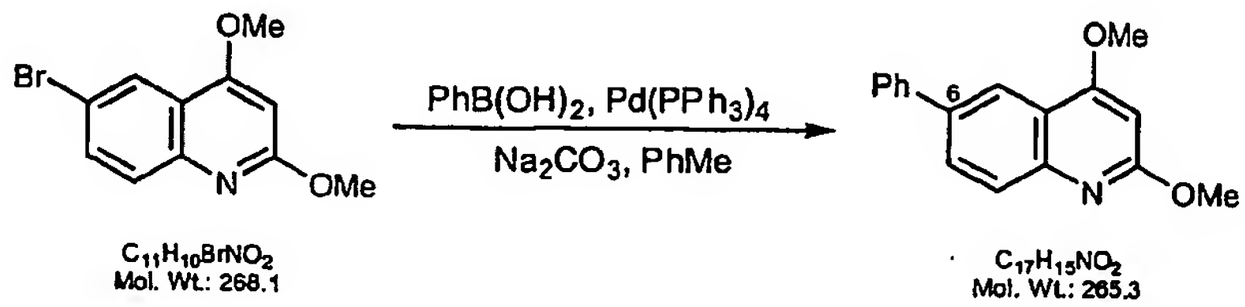
δ_H: 7.96 (1H, d, *J* 1.9, H8), 7.88 (1H, d, *J* 8.7, H5), 7.40 (1H, dd, *J* 8.7, 1.9, H6), 6.20 (1H, s, H3), 4.03 (3H, s, OMe), 3.97 (1H, s, OMe).

δ_C: 164.5, 163.8 (C2, C4), 148.0 (C8a), 129.4, 126.6, 124.1, 123.3, 117.7, 91.0 (C3), 55.8 (OMe), 53.6 (OMe).

n_{max}/cm^{-1}: 1618, 1596, 1574 (s, C=C, C=N), 1208 (s, C-O-C).

m/z: 269 (100%, M^+ ^{81}Br), 268 (88%, M^+ ^{81}Br - H), 267 (96%, M^+ ^{79}Br), 266 (87%, M^+ ^{79}Br - H), 239 (36%, M^+ ^{81}Br - CH_2O), 237 (33%, M^+ ^{79}Br - CH_2O).

EXAMPLE 61. 2,4-Dimethoxy-6-phenylquinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{17}H_{15}NO_2$
Mol. Wt.: 265.3

6-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 60**) (0.40 g, 1.5 mmol), benzeneboronic acid (0.20 g, 1.6 mmol), tetrakis(triphenylphosphine) palladium(0) (52 mg, 3 mol%), sodium carbonate (0.32 g in 1 ml H_2O), ethanol (0.5 ml) and toluene (8 ml) were heated at 80°C under argon for 48 hours. After cooling, ether (5 ml) and water (10 ml) were added, and the flask contents transferred to a separating funnel. The mixture was extracted with diethyl ether (3 x 30 ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown residue. Column chromatography (9:1 hexane : EtOAc) furnished the pure compound as a white powder. Yield 0.35 g, 88%. Melting point 121-123°C.

Found M^+: 265.1110. $C_{17}H_{15}NO_2$ requires 265.1103.

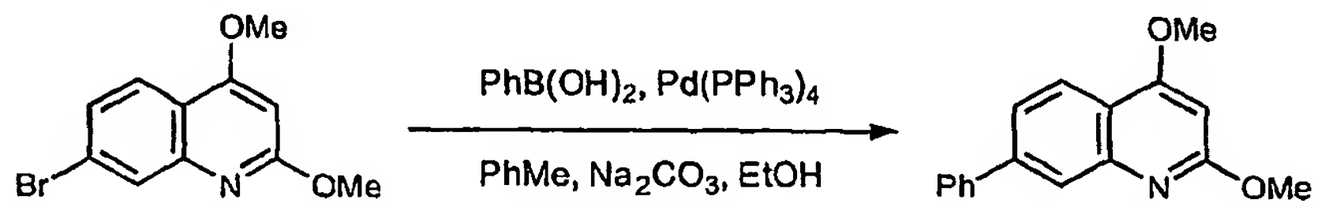
δ_H: 8.27 (1H, d, *J* 1.5, H5), 7.89-7.82 (2H, m, H8, H7), 7.70 (2H, dd, *J* 7.3, 1.4, H2' and H6'), 7.46 (2H, t, *J* 7.3, H3' and H5'), 7.35 (1H, dd, *J* 7.3, 1.4, H4'), 6.24 (1H, s, H3), 4.07 (3H, s, OMe), 4.00 (3H, s, OMe)

δ_C: 164.1, 164.0 (C2, C4), 146.5, 140.9, 136.1 (C1', C6, C8a), 129.3, 128.9, 127.3, 127.2, 127.1, 119.9, 119.4, 91.0 (C3), 55.8 (OMe), 53.5 (OMe).

n_{max}/cm^{-1}: 1626, 1600, 1580 (m, C=C, C=N), 1207 (s, C-O).

m/z: 265 (100%, M^+), 264 (62%, M^+ - H), 236 (19%), 235 (25%).

EXAMPLE 62. 2,4-Dimethoxy-7-phenyl quinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt: 268.1

$C_{17}H_{15}NO_2$
Mol. Wt: 265.3

7-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 60**) (0.10 g, 0.33 mmol), benzeneboronic acid (0.06 g, 0.5 mmol), tetrakis(triphenylphosphine) palladium (0) (13 mg, 0.011 mmol), aqueous sodium carbonate (80 mg, 0.74 mmol in 0.5 ml H_2O), ethanol (0.5 ml) and toluene (5 ml) were heated at 80°C under argon for 48 hours. After cooling, the reaction mixture was washed with water (20 ml) and extracted with ether (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure to give the crude product (a brown oil) which was purified by column chromatography (9:1 hexane:EtOAc), furnishing the title compound (R_f 0.40) as white prisms. Yield 80 mg, 84%. Melting point 118-120°C. (Found C: 76.96, H: 5.69, N: 5.14%. $C_{17}H_{15}NO_2$ requires C: 76.96, H: 5.70, N: 5.28%.)

Found M^+: 265.1096. $C_{17}H_{15}NO_2$ requires 265.1103.

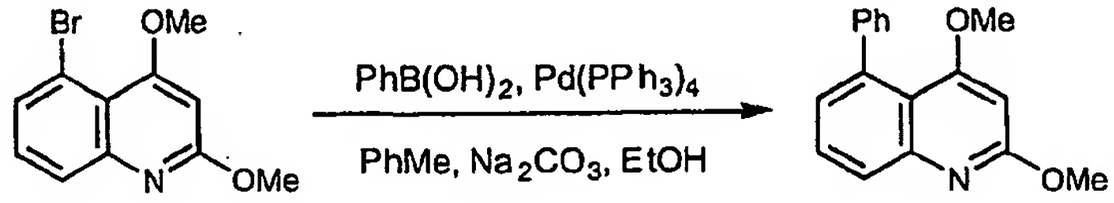
δ_H: 8.09 (1H, d, *J* 8.5, H5), 8.00 (1H, d, *J* 1.9, H8), 7.73 (2H, dd, *J* 7.1, 2.0, H2', H6'), 7.59 (1H, dd, *J* 8.5, 1.9, H6), 7.46 (2H, t, *J* 7.1, H3', H5'), 7.39-7.34 (1H, m, H4'), 6.21 (1H, s, H3), 4.07 (3H, s, OMe), 3.98 (3H, s, OMe).

δ_C: 164.3, 163.9 (C2, C4), 147.4, 142.7, 140.7 (C8a, C1', C7), 128.9, 127.7, 127.5, 124.8, 122.8, 122.4 (C2'+ 6', C3' + 5', C4', C5, C6, C8), 118.3 (C4a), 90.7 (C3), 55.8 (OMe), 53.5 (OMe).

n_{max}/cm^{-1}: 1617, 1610, 1578 (s, C=C, C=N), 1206 (s, C-O).

m/z: 265 (79%, M^+), 264 (41%, $M^+ - H$), 217 (22%), 213 (21%), 212 (22%), 201 (32%).

EXAMPLE 63. 2,4-Dimethoxy-5-phenylquinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{17}H_{15}NO_2$
Mol. Wt.: 265.3

5-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 59**) (0.15 g, 0.56 mmol), benzeneboronic acid (76 mg, 0.62 mmol), tetrakis(triphenylphosphine) palladium (0) (19 mg, 0.017 mmol, 3 mol%), aqueous sodium carbonate (0.12 g in 0.5 ml H_2O), ethanol (0.5 ml) and toluene (8 ml) were heated at 80°C for 48 hours. After cooling, the reaction mixture was washed with water (20 ml) and extracted with diethyl ether (3 x 30 ml). The combined organic extracts were dried, and the solvent removed under reduced pressure to give a brown oil. Column chromatography (9:1 hexane:EtOAc) furnished the pure quinoline (R_f 0.33) as white plates. Yield 0.12 g, 81%. Melting point 97-99°C. (Found C: 76.78, H: 5.54, N: 5.17%. $C_{17}H_{15}NO_2$ requires C: 76.96, H: 5.70, N: 5.28%.)

Found M^+: 265.1106. $C_{17}H_{15}NO_2$ requires 265.1103.

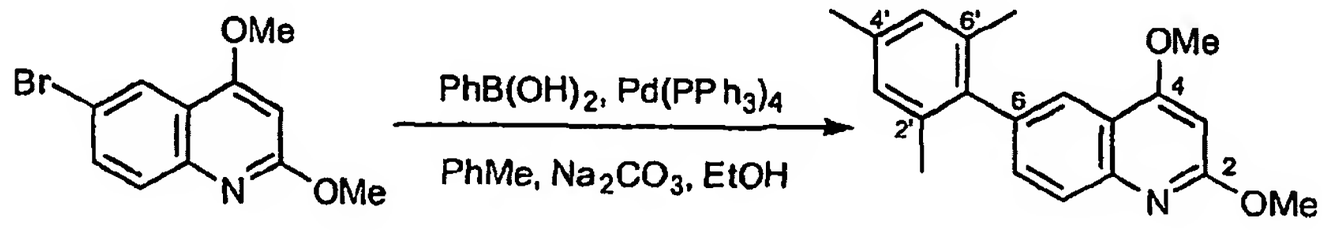
δ_H: 7.80 (1H, dd, *J* 8.3, 1.2, H8), 7.55 (1H, dd, *J* 8.3, 7.2, H7), 7.35-7.27 (5H, m, 5xArH), 7.13 (1H, dd, *J* 7.2, 1.2, H6), 6.14 (1H, s, H3), 4.06 (3H, s, 2-OMe), 3.48 (3H, s, 4-OMe).

δ_C: 165.6, 163.1 (C2, C4), 148.7, 144.7, 173.7 (C8a, C1', C5), 129.2, 127.9, 127.4, 127.3, 127.2, 126.5 (CH), 117.5 (C4a), 91.7 (C3), 55.4 (OMe), 53.8 (OMe).

n_{max}/cm^{-1}: 1612, 1581 (s, C=C, C=N), 1209 (s, C-O-C).

m/z: 265 (100%, M^+), 232 (33%), 164 (17%).

EXAMPLE 64. 2,4-Dimethoxy-6 (2',4',6'-trimethylphenyl)quinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{20}H_{21}NO_2$
Mol. Wt.: 307.4

6-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 58**) (0.40 g, 1.5 mmol), 2,4,6-trimethylbenzene-boronic acid (0.28 g, 1.7 mmol), tetrakis(triphenylphosphine) palladium (0) (52 mg, 3 mol%), sodium carbonate (0.32 g, 3 mmol in 1 ml H_2O), ethanol (0.5 ml) and toluene (9 ml) were heated at 80°C under argon for 48 hours. After cooling ether (5 ml) and water (10 ml) were added, and the flask contents transferred to a separating funnel. The mixture was extracted with diethyl ether (3 x 30 ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown solid. Column chromatography (9:1 hexane:EtOAc) yielded the pure arylquinoline (R_f 0.30) as a white powder. Yield 0.34 g, 74%. Melting point 199-201°C.

Found M^+: 308.1652. $C_{20}H_{22}NO_2$ requires 308.1651.

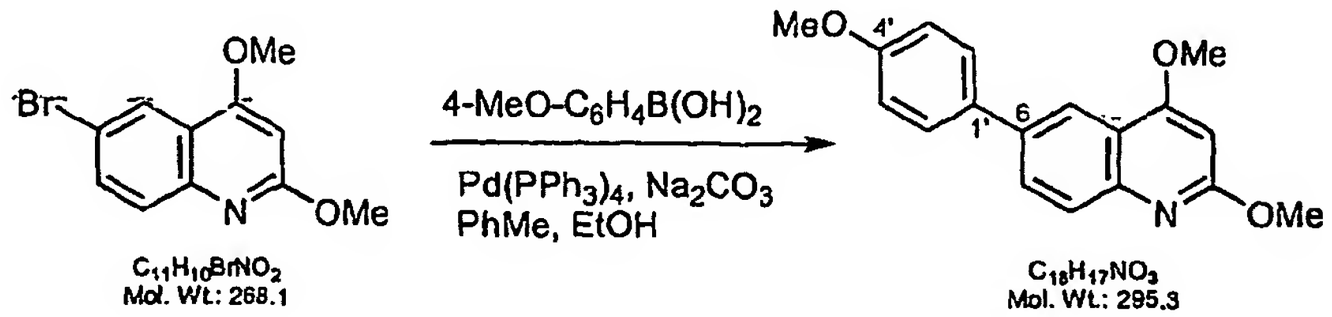
δ_H: 7.83 (2H, m, H5, H8), 7.39 (1H, d, *J* 8.6, 1.9, H7), 6.95 (2H, s, H3', H5'), 6.24 (1H, s, H3), 4.08 (3H, s, OMe), 3.96 (3H, s, OMe), 2.34 (3H, s, 6'-Me), 2.01 (6H, s, 2'-Me, 6'-Me).

δ_C: 164.4, 164.2 (C2, C4), 146.2 (C8a), 139.2, 137.0, 136.7 (C6, C1', C4'), 136.6 (C2', C6'), 132.2, 128.5, 127.3, 122.5 (C5, C7, C8, C3'+5'), 119.7 (C4a), 91.2 (C3), 56.1 (OMe), 53.9 (OMe), 21.5 (Me), 21.3 (Me).

n_{max}/cm^{-1}: 1624, 1598, 1574 (s, C=C, C=N), 1204 (s, C-O).

m/z: 308 (88%, M^+), 307 (55%, M^+ - H), 279 (100%, $M^+ - CH_3 + CH_2$), 190 (36%).

EXAMPLE 65. 2,4-Dimethoxy-6-(4'-methoxyphenyl)-quinoline



6-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 58**) (0.40 g, 1.5 mmol), (4-methoxybenzene)-boronic acid (0.25 g, 1.6 mmol), tetrakis(triphenylphosphine) palladium (0) (52 mg, 0.045 mmol, 3 mol%), aqueous sodium carbonate (0.32 g, 3 mmol in 1 ml H_2O), ethanol (1 ml) and toluene (8 ml) were heated at 80°C under argon for 48 hours. After cooling, water (20 ml) was added, and the mixture extracted with diethyl ether (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a brown oil. Column chromatography (4:1 hexane:EtOAc) gave the title compound (R_f 0.42) as white flakes. Yield 0.30 g, 68%. Melting point 107-109°C. (Found C: 72.96, H: 5.72, N: 4.64%. $C_{18}H_{17}NO_2$ requires C: 73.28, H: 5.80, N: 4.74%.)

Found M^+: 295.1203. $C_{18}H_{17}NO_2$ requires 295.1208.

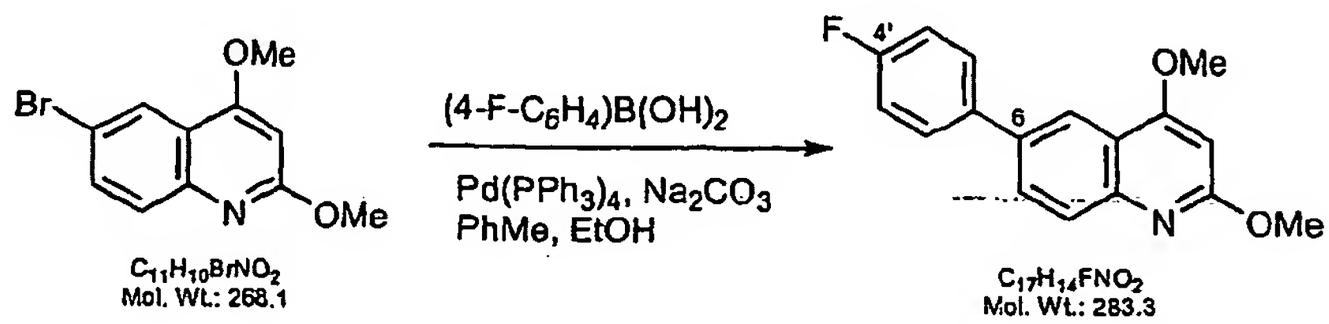
δ_H: 8.21 (1H, s, H5), 7.82 (2H, s, H7 and H8), 7.63 (2H, d, *J* 8.5, H2' and H6'), 6.99 (2H, d, *J* 8.5, H3' and H5'), 6.22 (1H, s, H3), 4.06 (3H, s, OMe), 3.99 (3H, s, OMe), 3.85 (3H, s, OMe).

δ_C: 164.4, 164.2 (C2, C4), 159.5 (C4'), 146.5 (C8a), 136.2, 133.9 (C6', C1'), 129.5 (CH), 128.7 (CH), 127.6 (CH), 119.8 (C4a), 119.5 (CH), 114.7 (CH), 91.4 (C3), 56.2 (OMe), 55.8 (OMe), 53.9 (OMe).

n_{max}/cm^{-1}: 1626, 1604, 1570 (s, C=C, C=N), 1210 (s, C-O).

m/z: 295 (100%, M^+), 278 (22%), 250 (12%), 133 (10%).

EXAMPLE 66. 2,4-Dimethoxy-6-(4'-fluorophenyl)-quinoline



6-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 65**) (0.40 g, 1.5 mmol), 4-fluorobenzeneboronic acid (0.25 g, 1.8 mmol),tetrakis(triphenylphosphine) palladium (0) (52 mg, 0.045 mmol, 3 mol%), aqueous sodium carbonate (0.32 g, 3 mmol in 1 ml H_2O), ethanol (1 ml) and toluene (10 ml) were heated at 80°C under argon for 48 hours. After cooling, water (20 ml) was added, and the mixture extracted with diethyl ether (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product, which was purified by column chromatography (4:1 hexane:EtOAc) to give the title compound (R_f 0.40) as a white powder. Yield 0.37 g, 87%. Melting point 115-117°C. (Found C: 72.04, H: 4.93, N: 4.63%. $C_{17}H_{14}FNO_2$ requires C: 72.07, H: 4.98, N: 4.94%.)

Found M^+: 283.1002. $C_{17}H_{14}FNO_2$ requires 283.1009.

δ_H: 8.20 (1H, d, *J* 1.9, H5), 7.84-7.78 (2H, m, H7, H8), 7.69-7.62 (2H, m, H2', H6'), 7.16-7.10 (2H, m, H3', H5'), 6.24 (1H, s, H3), 4.07 (3H, s, OMe), 4.00 (3H, s, OMe).

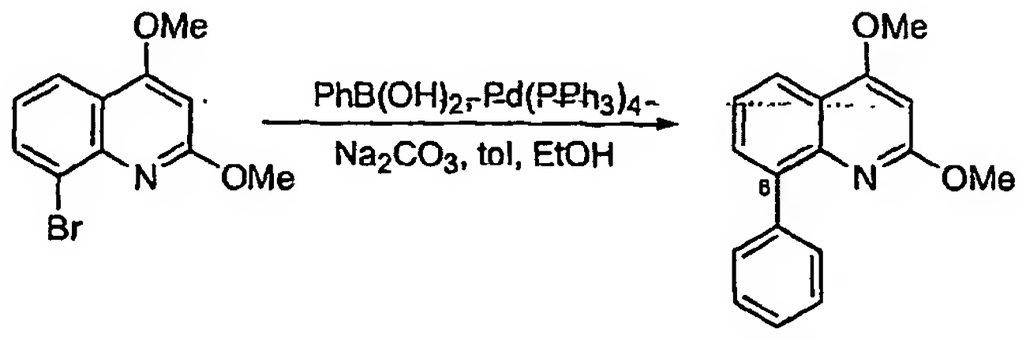
δ_C: 164.4, 164.3 (C2, C4), 162.8 (d, $^1J_{C\text{-}F}$ 246, C4'), 146.8 (C8a), 135.6, 132.5, 129.5, 129.1 (d, $^2J_{C\text{-}F}$ 20, C3', C5'), 127.8, 120.1, 119.8 (C4a), 116.2 (d, $^3J_{C\text{-}F}$ 8, C2', C6'), 91.5 (C3), 56.2 (OMe), 53.9 (OMe).

ν_{max}/cm^{-1}: 1626, 1603, 1569 (s, C=C, C=N), 1210 (s, C-O).

m/z: 283 (100%, M^+), 183 (32%).

EXAMPLE 67. 2,4-Dimethoxy-8-phenylquinoline

Method A - Tetrakis triphenylphosphine palladium (0) as catalyst.



$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{17}H_{15}NO_2$
Mol. Wt.: 265.3

8-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 53**) (0.40 g, 1.5 mmol) was dissolved in toluene (10 ml) under argon. Tetrakis(triphenylphosphine)-palladium (0) (52 mg, 3 mol%) and aqueous sodium carbonate (2.0 ml of a 2M solution) were added, and the mixture stirred for 5 minutes. Then benzeneboronic acid (0.20 g, 1.7 mmol) in ethanol (1 ml) was added, and the mixture was then heated under reflux for 48 hours. After cooling, the mixture was poured into a separating funnel, and the reaction flask washed with water (20 ml) and ether (20 ml), the washings being added to the separating funnel. The aqueous layer was extracted with ether (3 x 20 ml), and the combined organic layers were dried over magnesium sulfate before removal of the solvent under reduced pressure. The crude product was purified by column chromatography (9:1 hexane:EtOAc) to yield the title compound (R_f 0.43) as white plates. Yield 0.16 g, 40%. Melting point 76-78°C. (Found C: 76.34, N: 5.66, N: 5.02%. $C_{17}H_{15}NO_2$ requires C: 76.96, H: 5.70, N: 5.28%.)

Found M^+: 265.1105. $C_{17}H_{15}NO_2$ requires 265.1103.

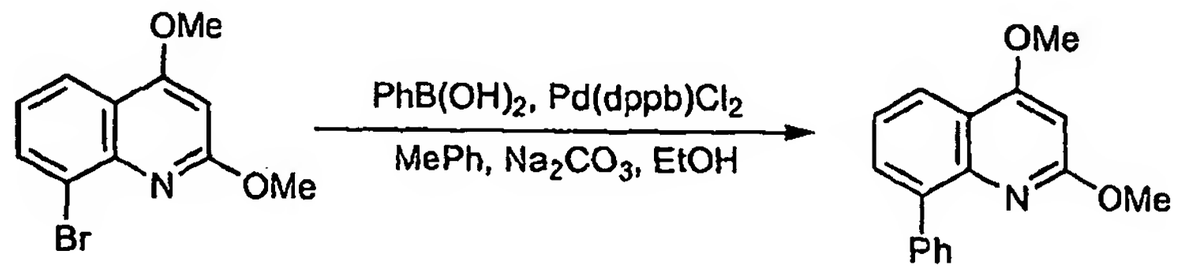
δ_H: 8.16 (1H, dd, *J* 8.2, 1.5, H5), 7.90 (2H, dd, *J* 8.3, 1.5, H2', H6'), 7.77 (1H, dd, *J* 7.2, 1.5, H7), 7.56-7.52 (2H, m, Ar-H), 7.49-7.43 (2H, m, Ar-H), 6.29 (1H, s, H3), 4.01 (3H, s, OMe), 3.99 (3H, s, OMe).

δ_C: 164.5, 163.4 (C2, C4), 144.7, 140.4, 138.5 (C1', C8, C8a), 131.3, 131.1, 127.9, 127.2, 123.5, 121.8 (C5, C6, C7, C2'-6'), 120.1 (C4a), 90.7 (C3), 56.2 (OMe), 53.8 (OMe).

n_{max} / cm^{-1}: 1619, 1583 (s, C=C, C=N), 1206 (s, C-O).

m/z: 265 (64%, M^+), 264 (100%, M^+ - H), 250 (7%, M^+ - CH_3), 188 (8%, M^+ - Ph).

Method B - 1,4-bis(diphenylphosphino)butane palladium (II) chloride as catalyst.

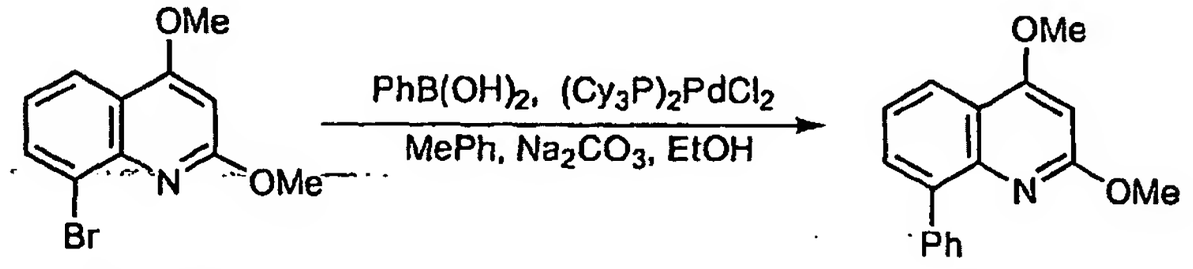


$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{17}H_{15}NO_2$
Mol. Wt.: 265.3

1,4-Bis(diphenylphosphinyl)butane (24 mg, 5.5 x 10^{-5} mol) was added, with stirring, to bis(benzonitrile) palladium (II) chloride (21 mg, 5.5 x 10^{-5} mol) in toluene (3 ml), and the mixture stirred for 20 minutes under argon to generate the required catalyst, 1,4-bis(diphenylphosphino)butane palladium (II) chloride, as an orange solid. Then 8-bromo-2,4-dimethoxyquinoline (**EXAMPLE 67**) (0.30 g, 1.1 mmol), benzeneboronic acid (0.15 g, 1.2 mmol), aqueous sodium carbonate (0.25 g dissolved in 1.0 ml H_2O), ethanol (0.5 ml) and a further 5 ml of toluene were added, and the mixture heated at 90°C for 48 hours. The mixture was washed with water, extracted with diethyl ether (3 x 30 ml), the combined organic extracts dried, and the solvent removed *in vacuo* to give a brown oil. Column chromatography (9:1 hexane:EtOAc) yielded the arylquinoline as a white powder. Yield 0.12 g, 40%. Spectral data as for compound prepared by method A.

Method C - bis(tricyclohexylphosphine)palladium(II) chloride as catalyst

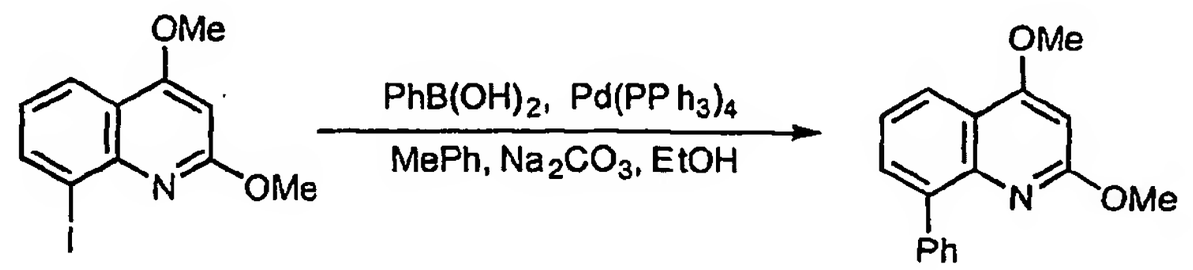


$C_{11}H_{10}BrNO_2$
Mol. Wt: 268.1

$C_{17}H_{15}NO_2$
Mol. Wt: 265.3

8-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 67**) (0.20 g, 0.75 mmol), benzeneboronic acid (0.10 g, 0.82 mmol), aqueous sodium carbonate (0.16 g, 1.5 mmol, in 0.5 ml H_2O), bis(tricyclohexylphosphine)palladium (II) chloride (28 mg, 5 mol%), ethanol (0.5 ml) and toluene (5 ml) were stirred at 90°C under argon for 48 hours. After cooling, water (15 ml) was added and the mixture transferred to as separating funnel. The reaction flask was washed with ether and the washings also transferred to the funnel. The aqueous layer was extracted with ether (2 x 20 ml), the combined organic extracts dried ($MgSO_4$), and the solvent removed *in vacuo* to give an orange residue. Column chromatography (9:1 hexane:EtOAc) furnished the title compound as white needles. Yield 0.11 g, 56%. Spectral data as for method A.

Method D - from the iodoquinoline.



$C_{11}H_{10}INO_2$
Mol. Wt: 315.1

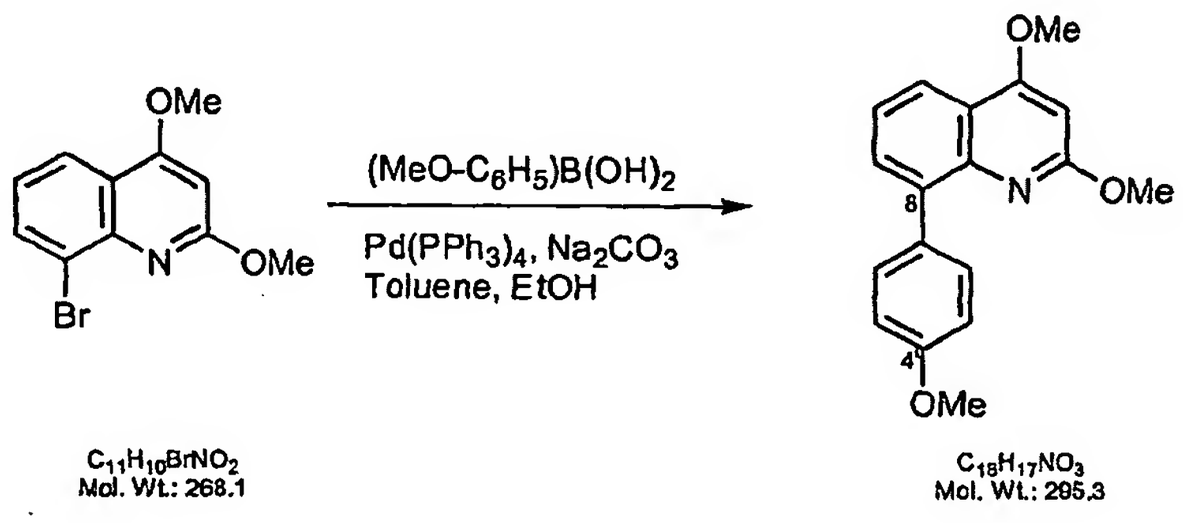
$C_{17}H_{15}NO_2$
Mol. Wt: 265.3

2,4-Dimethoxy-8-iodoquinoline (**EXAMPLE 55**) (0.40 g, 1.3 mmol), benzeneboronic acid (0.18 g, 1.5 mmol), tetrakis(triphenylphosphine)palladium (0) (45 mg, 3 mol%), aqueous sodium carbonate (0.32 g, 3.0 mmol, in 1 ml H_2O), ethanol (0.5 ml) and toluene (7 ml) were heated under reflux in an argon

atmosphere for 48 hours. Workup as in Method C. Yield after column chromatography (9:1 hexane:EtOAc) 0.14 g, 41%.

Spectral data in agreement with the compound prepared by method A.

EXAMPLE 68. 2,4-Dimethoxy-8-(4'-methoxyphenyl)quinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt: 268.1

$C_{18}H_{17}NO_3$
Mol. Wt.: 295.3

8-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 53**) (0.40 g, 1.5 mmol), (4-methoxybenzene)-boronic acid (0.25 g, 1.6 mmol), tetrakis(triphenylphosphine) palladium (0) (52 mg, 3 mol%), aqueous sodium carbonate (2.0 ml of a 2M solution), ethanol (1 ml) and toluene (10 ml) were heated at 90°C under argon for 48 hours. After cooling, water (20 ml) was added, and the mixture extracted with diethyl ether (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to give an orange oil, which was purified by column chromatography (9:1 hexane:EtOAc) to give white plates, R_f 0.29. Yield 0.14 g, 32%. Melting point 85-88°C. (Found C: 73.43, H: 5.84, N: 4.68%. $C_{18}H_{17}NO_3$ requires C: 73.20, H: 5.80, N: 4.68%.)

Found M^+: 295.1200. $C_{18}H_{17}NO_3$ requires 295.1208.

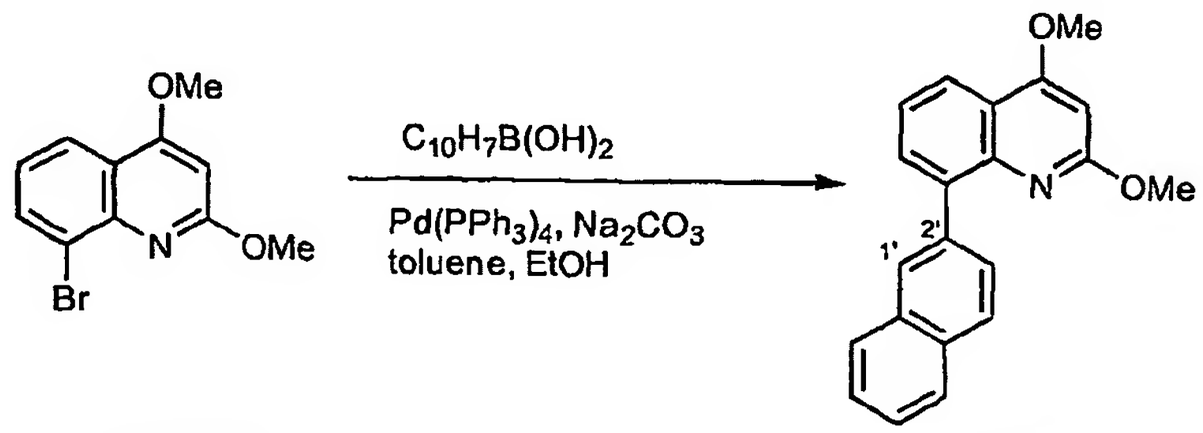
δ_H: 7.95 (1H, dd, *J* 8.2, 1.5, H5), 7.67 (2H, d, *J* 8.8, H2' and H6'), 7.57 (1H, dd, *J* 7.2, 1.5, H7), 7.29 (1H, dd, *J* 8.2, 7.2, H6), 6.91 (2H, d, *J* 8.8, H3' and H5'), 6.15 (1H, s, H3), 3.90 (3H, s, OMe), 3.84 (3H, s, OMe), 3.79 (3H, s, OMe).

δ_C: 164.5, 163.3, 159.0 (C2, C4, C4'), 144.7, 138.0, 132.8 (C8a, C8, C1'), 132.2 (CH), 130.9 (CH), 123.5 (CH), 121.3 (CH), 120.1 (C4a), 113.4 (CH), 90.6 (C3), 56.2 (OMe), 55.7 (OMe), 53.8 (OMe).

n_{max} / cm^{-1}: 1618, 1582 (s, C=C, C=N).

m/z: 295 (100%, M^+), 294 (93%, M^+ - H), 214 (82%), 199 (46%).

EXAMPLE 69. 2,4-Dimethoxy-8-(2'-naphthyl)quinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{21}H_{17}NO_2$
Mol. Wt.: 315.4

8-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 53**) (0.40 g, 1.5mmol), 2-naphthylboronic acid (0.30 g, 1.7 mmol), $Pd(PPh_3)_4$ (52 mg, 3 mol%), aqueous sodium carbonate (2.0 ml of a 2M solution), ethanol (1 ml) and toluene (10 ml) were heated at 85°C under argon for 48 hours. The cooled reaction mixture was washed with water (20 ml), and extracted with diethyl ether (3 x 30 ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil. Column chromatography (9:1 hexane:EtOAc) furnished the pure naphthylquinoline as white plates (R_f 0.40), yield 0.3 g, 63%. Melting point 127-129°C. (Found C: 79.62, H: 5.52, N: 4.28%. $C_{21}H_{17}NO_2$ requires C: 79.98, H: 5.43, N: 4.44%.)

Found M^+: 315.1255. $C_{21}H_{17}NO_2$ requires 315.1259.

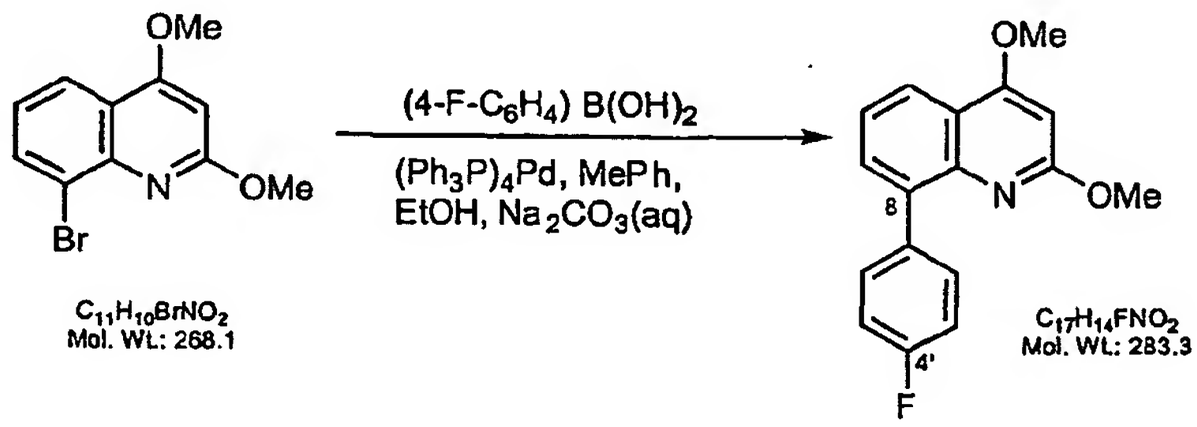
δ_H: 8.19 (1H, d, *J* 1.4, H1'), 8.10 (1H, dd, *J* 8.2, 1.5, H5), 7.99 (1H, dd, *J* 8.6, 1.7, Np-H), 7.89-7.87 (3H, m, Ar-H), 7.78 (1H, dd *J* 7.2, 1.5, H7), 7.49-7.40 (3H, m, Ar-H), 6.24 (1H, s, H3), 3.99 (3H, s, OMe), 3.87 (3H, s, OMe).

δ_C: 164.2, 163.1 (C2, C4), 144.5 (C8a), 138.0, 137.8, 133.5, 132.5, 131.2 (CH), 129.6 (CH), 129.1 (CH), 128.2 (CH), 127.6 (CH), 126.4 (CH), 125.8 (2 x CH), 123.2 (CH), 121.6 (CH), 119.8, 90.4 (C3), 55.8 (OMe), 53.5 (OMe).

n_{max} /cm^{-1}: 1618, 1591, 1577 (s, C=C, C=N), 1209 (s, C-O).

m/z: 315 (100%, M^+), 314 (99%, M^+ - H), 300 (11%, M^+ - Me), 189 (39%, $C_{11}H_{11}NO_2^+$).

EXAMPLE 70. 8-(4'-Fluorophenyl)-2,4-dimethoxyquinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt: 268.1

$C_{17}H_{14}FNO_2$
Mol. Wt: 283.3

8-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 53**) (0.40 g, 1.5 mmol), 4-fluorobenzeneboronic acid (0.25 g, 1.8 mmol), tetrakis(triphenylphosphine) palladium (0) (52 mg, 3 mol%), aqueous sodium carbonate (2.0 ml of a 2M solution), ethanol (1 ml) and toluene (10 ml) were heated at 90°C under argon for 48 hours. The product was obtained after aqueous workup and ether extraction as a pale brown oil. After leaving to stand overnight, the oil crystallised to give pale orange prisms. Recrystallisation from hexane gave colourless prisms. Yield 0.15 g, 35%. Melting point: 108-110°C.

Found M^+: 283.1013. $C_{17}H_{14}FNO_2$ requires 283.1009.

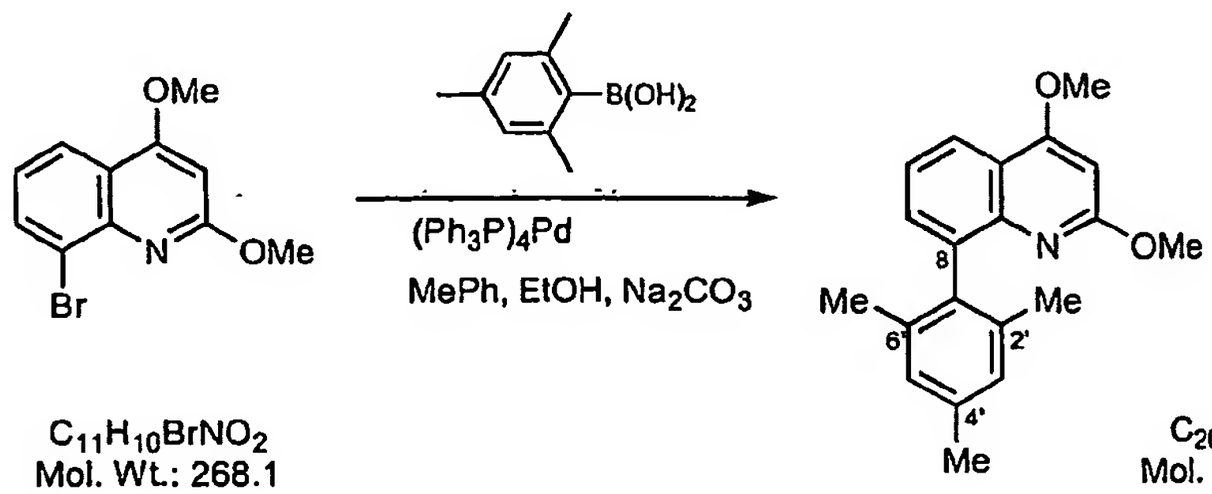
δ_H: 8.09 (1H, dd *J* 8.2, 1.5, H5), 7.79-7.75 (2H, m, H2', H6'), 7.65 (1H, dd *J* 7.3, 1.5, H7), 7.40 (1H, dd *J* 8.2, 7.3, H6), 7.18-7.13 (2H, m, H3', H5'), 6.26 (1H, s, H3), 4.02 (3H, s, OMe), 3.92 (3H, s, OMe).

δ_C: 164.1, 163.0 (C2, C4), 162.1 (d, $^1J_{C-F}$ 246, C4'), 144.2 (C8a), 137.0, 135.8, 132.2 (d, $^3J_{C-F}$ 8, C2', C6'), 130.7, 123.0, 121.5 (C5, C6, C7), 119.7, 114.3 (d, $^2J_{C-F}$ 21, C3', C5'), 90.3, 55.8 (OMe), 53.3 (OMe).

n_{max} /cm^{-1}: 1620, 1582 (s, C=C, C=N), 1206 (s, C-O).

m/z: 283 (79%, M^+), 282 (100%, M^+ - H), 253 (13%), 188 (8%, M^+.- C_6H_4F).

EXAMPLE 71. 2,4-Dimethoxy-8-(2',4',6'-trimethylphenyl)quinoline



$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{20}H_{21}NO_2$
Mol. Wt.: 307.4

8-Bromo-2,4-dimethoxyquinoline (**EXAMPLE 53**) (0.40 g, 1.5 mmol), 2,4,6-trimethylbenzene-boronic acid (0.28 g, 1.7 mmol), tetrakis(triphenylphosphine) palladium (0) (52 mg, 3 mol%), aqueous sodium carbonate (2.0 ml of a 2M solution), ethanol (1 ml) and toluene (10 ml) were heated at 90°C under argon for 48 hours. After workup by the usual method a brown oil was obtained. Column chromatography (9:1 hexane:EtOAc) yielded the title compound as white plates, yield 80 mg, 17%, R_f 0.55. (0.2 g of the reduced 2,4-dimethoxyquinoline was also obtained). Melting point 112-114°C. (Found C: 77.47, H: 6.77, N: 4.45%. $C_{20}H_{21}NO_2$ requires C: 78.15, H: 6.89, N: 4.56%.)

Found M^+: 307.1571. $C_{20}H_{21}NO_2$ requires 307.1572.

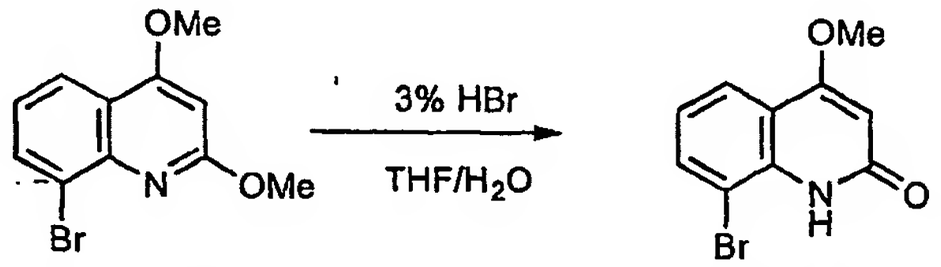
δ_H: 8.06 (1H, dd, *J* 7.7, 2.0, H5), 7.41-7.34 (2H, m, H6 and H7), 6.94 (2H, s, 3'H and 5'H), 6.19 (1H, s, H3), 3.98 (3H, s, OMe), 3.66 (3H, s, OMe), 2.35 (6H, s, 2'Me and 6'Me), 1.90 (3H, s, 4'Me).

δ_C: 164.2, 162.9 (C2, C4), 145.3 (C8a), 138.3, 137.5, 136.6, 136.0 (4 x quaternary C), 131.3, 127.6, 123.1, 121.0 (4 x Ar-H), 119.6, (C4a) 90.5 (C3), 55.9 (OMe), 53.2 (OMe), 21.3 (4'Me), 20.8 (2'Me, 6'Me).

n_{max} / cm^{-1}: 1618, 1586, 1583 (s, C=C, C=N).

m/z: 307, (59%, M^+), 292 (100%, M^+ - Me), 277 (14%).

EXAMPLE 72. 8-Bromo-4-methoxy 1*H*-quinolin-2-one



$C_{11}H_{10}BrNO_2$
Mol. Wt.: 268.1

$C_{10}H_8BrNO_2$
Mol. Wt.: 254.1

8-Bromo-2,4-dimethoxyquinoline (**Example 53**) (0.60 g, 2.2 mmol) was heated in 3% hydrobromic acid in 1:1 THF:water (32 ml) under reflux for 4 hours. The cooled solution was neutralised with sodium carbonate, and the THF removed *in vacuo* to precipitate the organic products. The precipitate was filtered off and dried under suction, and then subjected to a continuous (Soxhlet) extraction with hexane for 6 hours. Unreacted starting material (0.15 g) was recovered from the hexane. The quinolin-2-one product, white flakes, remained undissolved in the extraction thimble. Yield 0.38 g, 67%. Melting point >250°C.

Found M^+: 252.9734. $C_{10}H_8{}^{79}BrNO_2$ requires 252.9738.

δ_H: 8.76 (1H, br s, NH), 7.86 (1H, dd, *J* 8.1, 1.0, H5), 7.70 (1H, dd, *J* 7.8, 1.0, H7), 7.07 (1H, dd, *J* 8.1, 7.8, H6), 5.95 (1H, s, H3), 3.97 (3H, s, OMe).

δ_C: 164.2, 163.5, 135.4 (C8a), 134.3, 122.8, 122.7 (C5, C6, C7), 117.1, 108.9, 96.9 (C3), 56.4 (OMe).

n_{max}/cm^{-1}: 3383 (m, N-H), 1681 (s, C=O), 1592 (m, C=C).

m/z: 255 (97%, M^+ ^{81}Br), 253 (100%, M^+ ^{79}Br), 212 (23%, M^+ ^{81}Br - CONH), 210 (25%, M^+ ^{79}Br - CONH), 116 (18%).

BIOLOGICAL TESTING

(I) ANTHELMINTIC ACTIVITY

The anthelmintic properties of a number of compounds of the invention were tested against a benzimidazole sensitive *Haemonchus contortus* isolate. This assay is an *in vitro* larval development assay that is applicable to all parasitic nematodes with free-living life cycle stages.

(i) Activity against *Haemonchus contortus*

In the *Haemonchus contortus* assay, the eggs of parasitic nematodes are applied to the wells of a microtitre plate containing the test compound. After the eggs hatch, L1 larvae develop through to the L3 stage. Development of the larvae can be inhibited at a number of stages by nematocides. The morphology and stages of inhibition are highly characteristic for common modes of action and offer additional pharmacological criteria for the uniqueness of the activity observed. These observations are extremely informative where the assay is used as a primary screen for anthelmintic activity (Gill, J.H *et al*, Int. J. Parasit. (1991), 21, 771-776 and Gill, J.H. *et al*, Int. J. Parasit. (1995), 25, 463-470).

Protocol

Samples of compounds were weighed and dissolved by addition of dimethylsulfoxide (DMSO) to give a final stock concentration of 10,000 µg/ml. If a compound was not soluble at this concentration, the suspension was gently warmed to achieve dissolution. Compounds failing to dissolve were then diluted to 5,000 µg/ml and warmed. Poorly soluble compounds were handled by repeated dilution and warming until the dissolution was complete as possible.

Twelve serial ½ dilutions in DMSO solution were prepared from each stock solution, each of which was then diluted 1/5 with water. Aliquots (10 µl) of each dilution were transferred to the bioassay plates and diluted a further 20-fold with

agar (2%, 190 µl) to give a final concentration range of 0.045 to 100 µg/ml (2,048-fold range), or a corresponding range for compounds where the stock concentration was lower than 10,000 µg/ml. Any precipitation was found to redissolve upon addition of hot agar.

Test Organism

The McMaster isolate of *H. contortus* is a reference susceptible strain routinely maintained by passage in sheep; this isolate has had little, if any, exposure to any anthelmintic. Nematodes eggs were isolated from the faeces of infested animals according to standard literature procedures.

Procedure

The effect of the test compounds on larval development was determined in the assay described by Lacey *et al* (1990), "A larval development assay for the simultaneous detection of broad spectrum anthelmintic resistance" in "*Resistance of Parasites to Antiparasitic Drugs*", Round Table Conference held at the VII International Congress of Parasitology, Paris, August, 1990 (Edited by Boray, J.C, Martin, P.J and Roush, R.P.), pp177-184, MSD AGVET, Rahway, NJ, USA). Briefly, 80 to 100 nematode eggs were added to the surface of the agar matrix containing the test compound, supplemented with a nutrient medium and incubated at 26°C until larvae in the control (no drug) wells developed to the L3 stage. A qualitative assessment of the larvae in each well was made on Day 5 of the assay (see Column "NeT" in Table 1). The wells for each dilution of every compound (from highest to lowest concentration) were inspected to determine the well number corresponding to the lowest concentration at which development was inhibited in 99% of the nematode larvae present. As the well numbers correspond to a two-fold serial dilution of each compound, a titre (dilution factor) is generated as 2^{n-1}, where n is the well number. By dividing the highest concentration by the titre, an LD_{99} value was obtained, representing the concentration required to inhibit development in 99% of the nematode larvae present.

The results of the assay for a selection of compounds are shown in Table 1. The nematocidal activity of the compounds in Table 1 are given as LD_{99} values in µg/ml, and represents the concentration required to inhibit development of 99% of *Haemonchus contortus* larvae.

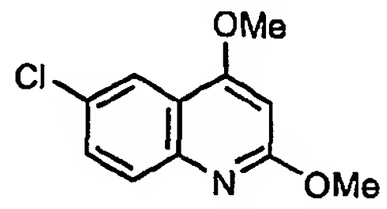
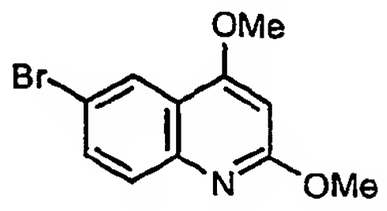
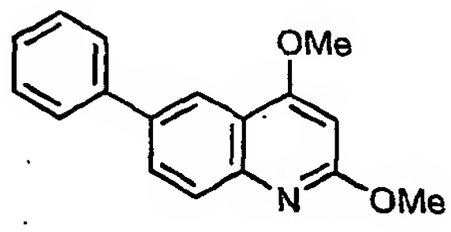
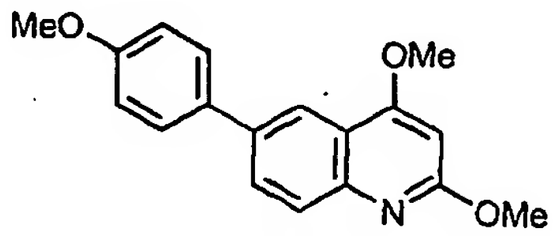
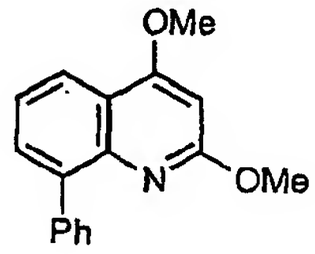
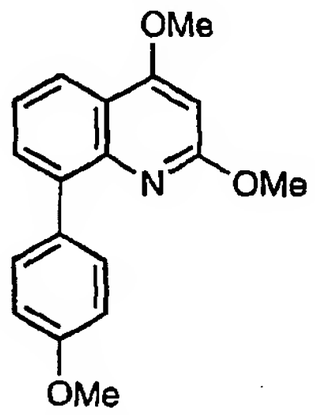
EXAMPLE NO.	STRUCTURE	NeT	LD_{99}/µg/ml
37		2	12.5
58		8	12.5
61		32	3.1
65		32	3.1
67		8	12.5
68		8	12.5

Table 1. Anthelmintic activity data

The data in Table 1 indicate that representative compounds of the invention, 37, 58, 51, 65. 67 and 68, possess high nematocidal activity.

(ii) Activity against *Schistosoma mansoni cercariae*

The anthelmintic properties of a number of compounds of the invention were tested against recently released cercarial larvae of the human schistosome trematode, *Schistosoma mansoni*. The assay monitored cercarial behaviour changes and death as determined by a cessation of larval movement.

PROTOCOL

Samples of compounds were weighed and dissolved in ethanol to provide 50 mM stock solutions. These were serially diluted in ethanol (1:1 by volume) to provide a range of stock concentrations from 50 mM downwards.

In tests, these were added at a 1:99 dilution, to provide a range of in-well concentrations in the series 500 µM, 250 µM, 125 µM etc., to cercariae in 1 ml of water in 12 well tissue culture plates (Linbro). This dilution protocol produces a maximum in-well concentration of ethanol of 1% by volume, which does not significantly affect cercarial behaviour or longevity.

Cercariae of *S. mansoni* were obtained through the maintenance of the parasite life cycle in NMRI strain laboratory mice and *Biomphalaria glabrata* snails. Infected snails were induced to shed cercariae by exposure of water at 28°C and bright light. Approximately 30 cercariae were placed in each test well within 2 hours of their release from the snail hosts. For each compound and concentration, assays were set up in duplicate and repeated 3 times with different populations of cercariae. For each assay, the cercariae were observed with low power microscopy to assess cercarial activity 30 minutes after exposure to the test compound. At this time, the number of immobile cercariae In each well was counted and then all cercariae fixed and stained with Lugol's iodine to assess the percentage of cercariae that were immobile and presumed dead. Results from

the dilution series were employed to estimate the LD_{50} (30 minutes) for each compound. The results from this assay are shown in Table 2.

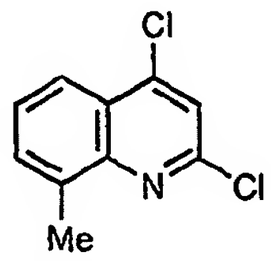
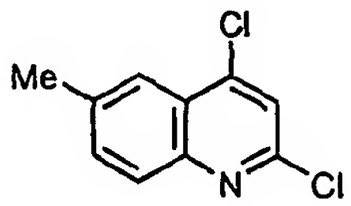
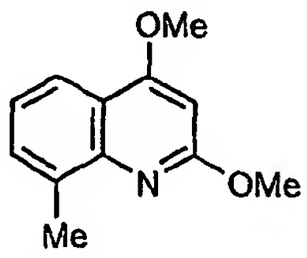
EXAMPLE NO.	STRUCTURE	LD_{50} (30 minutes)/μM
9		15
10		30
22		30

Table 2. Activity against *S. mansoni cercariae*

(iii) Activity against *Caenorhabditis elegans*

The anti-nematode properties of a number of compounds of the invention were tested against the free-living nematode *Caenorhabditis elegans*. The assay monitored behavioural changes and death as determined by complete cessation of movement by the worms.

PROTOCOL

Samples of compounds were weighed and dissolved in ethanol to provide 50 mM stock solutions. These were serially diluted in ethanol (1:1 by volume) to provide a range of stock concentrations from 50 mM downwards.

In tests, 20 µl of these stock solutions were added to 1.98 ml of *C. elegans* suspension in lidded glass vials to give a final dilution of 1:99. This gives a range of in-well concentrations in the series 500 µM, 250 µM, 125 µM, etc. This dilution protocol produces a maximum in-well concentration of ethanol of 1% by volume which does not significantly affect nematode behaviour or longevity.

C. elegans were maintained in culture of agar plates seeded with *Escherischia coli* bacteria. The nematodes were harvested 7 days after inoculation, into 0.05 M phosphate buffer – pH 7, and counted. The volume of the suspension was adjusted to give about 500 nematodes/ml. Aliquots of 1.98 ml were dispensed into glass vials and 20 µl of drug stock solution added. After 60 minutes, five samples of 100 µl were removed, and in each of these, the total number of nematodes and the number that were inactive were counted. From these five replicated values the mean percentage of immobile, presumed dead, nematodes associated with each concentration could be estimated. Results from dilution series were used to estimate the LD_{50} (60 minutes) for each compound. The results from this assay are shown in Table 3.

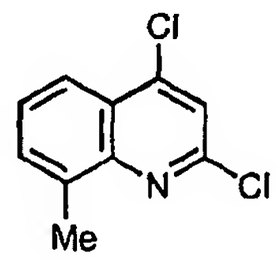
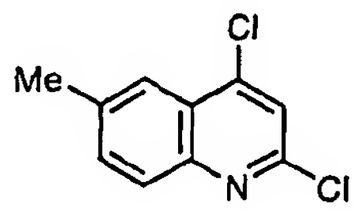
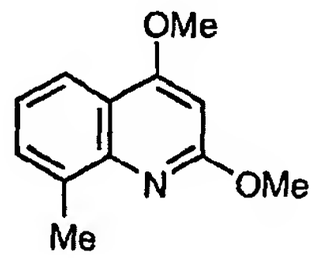
EXAMPLE NO.	STRUCTURE	LD_{50} (60 minutes)/µM
9		300
10		1.5
22		70

Table 3. Activity against C. *elegans*

(III) ECTOPARASITIC ACTIVITY

A number of compounds of the invention were tested against certain species of ectoparasites in accordance with the following bioassay protocols.

(i) Activity against *Lucilia cuprina*

(a). Topical application to adult male *Lucilia cuprina*

Adult male blowflies aged between 3 and 7 days of the species *L. cuprina* were lightly anaesthetised to permit handling, and 1 microlitre of the test solution, at a range of dilutions, was applied to the dorsal thorax. Four replicates of 15 blowflies were treated at each test dilution. A control group, treated with the solvent alone, was included for comparative purposes.

The treated blowflies and the controls were maintained in recovery containers under appropriate rearing conditions for 48 hours. Percentage mortality, as determined by no response of the adult blowfly if touched, was recorded at 24 and 48 hours after treatment (Table 4).

(b). Mortality test for larval *Lucilia cuprina*

First stage larvae, less than 24 hours of age, were placed on a surface that had been impregnated with the serial dilutions of the test compound. Four replicates of 50 larvae were exposed at each dilution. A control group, treated with the solvent alone, was included for comparative purposes.

The exposed larval blowflies were held in appropriate rearing conditions for 24 hours. Percentage mortality was recorded at 24 hours by counting dead and live larvae (Table 4).

(c). Insect growth regulator (IGR) test for larval *Lucilia cuprina*

First stage larvae, less than 24 hours of age, were placed on prepared media that had been impregnated with serial dilutions of the test compound. Four replicates of 100 larvae were exposed at each dilution. A control group, treated with the solvent alone, was included for comparative purposes.

The exposed larval blowflies were held in appropriate rearing conditions and were checked periodically. Just prior to pupation, the test lids on the holding containers were removed and the holding containers placed on a layer of sand to facilitate migration and pupation of the larvae. Percentage mortality and percentage IGR activity were recorded weekly (Table 4).

EXAMPLE NO.	Adult males	Larvae	
	% mortality	% mortality	% IGR effect
37	5.0	4.5	0
56	5.0	0	0
58	3.3	3.4	0
61	3.3	0	0
65	1.7	1.6	0
67	1.7	22.1	NT
68	3.3	31.6	NT

NT = not tested

Table 4. Results of bioassays against *Lucilia cuprina*

(ii) Activity against the cattle tick *Boophilus microplus*

(a). Injection test for engorged female *Boophilus microplus*

Engorged female ticks of *Boophilus microplus* were injected, through the cuticle between the mouthparts and first leg, with 1 microlitre of the test compound in a range of dilutions. Four replicates of 15 ticks were treated at each dilution. A control group, treated with the solvent alone, was included for comparative purposes.

The treated ticks were maintained at 25 ± 1°C for 14 days. Mortality and oviposition were recorded at 7 and 14 days. The results were recorded for either percentage mortality or percentage inhibition of oviposition (Table 5).

EXAMPLE NO.	% inhibition of oviposition
37	24.4
56	17.3
58	34.8
61	50.0
65	14.0
67	0
68	17.9

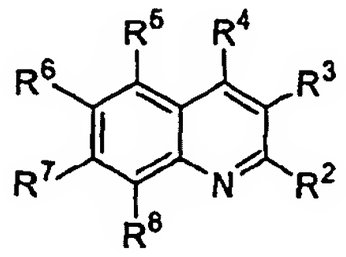
Table 5. Activity against *Boophilus microplus*

The data in Tables 4 and 5 indicate that all compounds have a low level of activity against adult *Lucilia cuprina*. Two compounds, i.e. 67 and 68, demonstrated a good level of activity against this larval stage of the life cycle of *Lucilia cuprina*.

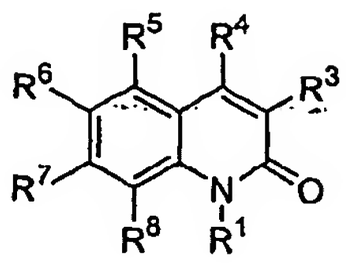
None of the compounds tested demonstrated any insect growth regulator activity at the concentrations tested against larval *Lucilia cuprina*. All test compounds, with the exception of compound 67, demonstrated moderate to good activity against the cattle tick, *Boophilus microplus*, with particularly good activity being demonstrated by compound 61. It should be noted that compound 68 demonstrated activity against both larval *Lucilia cuprina* and adult *Boophilus microplus*, thus demonstrating activity against both an insect and acarine ectoparasite.

CLAIMS

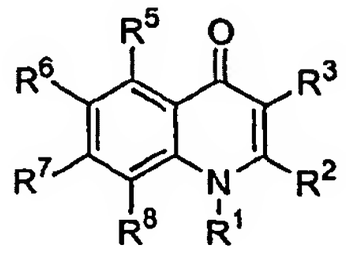
1. The use of a compound of Formula (I), (IA) or (IB):



(I)



(IA)



(IB)

in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of infections caused by parasitic helminths or arthropod ectoparasites, wherein:

R^1 represents H, C_1 to C_6 alkyl or benzyl;

R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of: C_6 to C_{10} aryl, CN, F, Cl, Br, I, OH, SH, NO_2, OR^9, SR^9, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_{20} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_2 to C_{10} alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6

to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(v) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{15} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(vi) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(vii) a heterocyclic group which may be aromatic or non-aromatic having from 5 to 10 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen or sulfur atoms and the remainder are carbon atoms;

(viii) OR^{12};

(ix) a halo group selected from F, Cl, Br or I;

(x) $NR^{10}R^{11}$;

(xi) $COOR^{10}$;

(xii) NO_2;

(xiii) SR^{12};

(xiv) $CONR^{10}R^{11}$;

(xv) COR^9;

(xvi) CN;

(xvii) OH; or

(xviii) SH,

wherein:

R^9 represents C_1 to C_6 alkyl or C_6 to C_{15} aryl;

R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of hydrogen, C_1 to C_6 alkyl and C_6 to C_{15} aryl; and

R^{12} represents C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

or an N-oxide derivative thereof, wherein the quinoline ring nitrogen forms an N-oxide group, or a pharmaceutically acceptable salt, solvate or quaternary ammonium salt thereof, with the proviso that (a) at least one of R^2 and R^4 is other than hydrogen and (b) for the compounds of Formula (IA) wherein R^3 represents dimethylallyl and R^4 represents ethoxy, at least one of R^5, R^6, R^7 and R^8 is other than hydrogen.

2. The use according to Claim 1 wherein R^2 represents

(i) C_1 to C_6 alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, CN, F, Cl, Br, I, OH, SH, NO_2, OR^9, SR^9, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(ii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(iii) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(iv) OR^{12};

(v) a halo group selected from F, Cl, Br or I;

(vi) $NR^{10}R^{11}$;

(vii) $COOR^{10}$;

(viii) SR^{12};

(ix) $CONR^{10}R^{11}$;

(x) COR^9; or

(xi) CN

wherein R^9, R^{10}, R^{11} and R^{12} are as defined as in Claim 1.

3. The use according to Claim 2 wherein R^2 represents

(i) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched;

(ii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OCF_3, CF_3, OR^9 or SR^9;

(iii) OR^{12};

(iv) a halo group selected from F, Cl, Br or I;

(v) $COOR^{10}$; or

(vi) COR^9

wherein R^9, R^{10} and R^{12} are as defined as in Claim 1.

4. The use according to Claim 3 wherein R^2 represents

(i) OR^{12}, wherein R^{12} is as defined as in Claim 1; or

(ii) a halo group selected from F, Cl, Br or I.

5. The use according to Claim 4 wherein R^2 represents

(i) OR^{12} wherein R^{12} represents unsubstituted C_1 to C_6 alkyl, which may be branched, or unbranched; or

(ii) a halo group selected from F, Cl, Br or I.

6. The use according to Claim 5 wherein R^2 represents methoxy or halo.

7. The use according to any preceding claim wherein R^3 represents

(i) hydrogen;

(ii) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, CN, F, Cl, Br, I, OH, SH, NO_2, OR^9, SR^9, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_{20} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9 or SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(v) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(vi) OR^{12} wherein R^{12} represents C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2 and $NR^{10}R^{11}$ wherein R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of hydrogen, C_1 to C_6 alkyl and C_6 to C_{15} aryl; or

(vii) a halo group selected from F, Cl, Br or I,

wherein unless stated otherwise, R^9, R^{10}, R^{11} and R^{12} are as defined as in Claim 1.

8. The use according to any preceding claim wherein R^3 represents

(i) hydrogen;

(ii) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched

(iii) unsubstituted C_6 to C_{15} aryl;

(iv) OR^{12} wherein R^{12} represents C_1 to C_6 alkyl; or

(v) a halo group selected from F, Cl, Br, I.

9. The use according to any preceding claim wherein R^3 represents hydrogen or halo.

10. The use according to any preceding claim wherein R^3 represents hydrogen.

11. The use according to any preceding claim wherein R^4 represents

(i) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO^2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(ii) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(iii) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(iv) OR^{12} wherein R^{12} represents C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(v) a halo group selected from F, Cl, Br or I;

(vi) $NR^{10}R^{11}$;

(vii) $COOR^{10}$;

(viii) SR^{12};

(ix) $CONR^{10}R^{11}$;

(x) COR^9; or

(xi) CN,

wherein R^9, R^{10}, R^{11} and R^{12} are as defined as in Claim 1.

12. The use according to Claim 11 wherein R^4 represents

(i) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched;

(ii) unsubstituted C_6 to C_{10} aryl;

(iii) OR^{12};

(iv) a halo group selected from F, Cl, Br or I;

(v) $COOR^{10}$; or

(vi) COR^{9},

wherein R^{8}, R^{10} and R^{12} are as defined as in Claim 1.

13. The use according to Claim 12 wherein R^{4} represents

(i) OR^{12} wherein R^{12} is as defined as in Claim 1; or

(ii) a halo group selected from F, Cl, Br or I.

14. The use according to Claim 13 wherein R^{4} represents

(i) OR^{12} wherein R^{12} represents unsubstituted C_1 to C_6 alkyl, which may be branched, or unbranched; or

(ii) a halo group selected from F, Cl, Br or I.

15. The use according to Claim 14 wherein R^{4} represents methoxy or halo.

16. The use according to any preceding claim wherein R^{5}, R^{6}, R^{7} and R^{8} are each independently selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_{20} alkyl, which may be branched, or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^{9}, SR^{9}, CN, F, Cl, Br, I, OH, SH, NO_2, COR^{9}, $COOR^{10}$, and $NR^{10}R^{11}$;

(iii) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^{9}, SR^{9}, CN, F, Cl, Br, I, OH, SH, NO_2, COR^{9}, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(iv) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^{9}, SR^{9}, CN, F, Cl, Br, I, OH, SH, NO_2, COR^{9}, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(v) a heterocyclic group having from 5 to 10 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen or sulfur atoms and the remainder are carbon atoms;

(vi) OR^{12};

(vii) a halo group selected from F, Cl, Br or I;

(viii) COR^{9};

(ix) CN; and

(x) OH,

wherein R^{9}, R^{10}, R^{11} and R^{12} are as defined as for Claim 1.

17. The use according to Claim 16 wherein R^{5}, R^{6}, R^{7} and R^{8} are each independently selected from the group consisting of:

(i) hydrogen

(ii) unsubstituted C_1 to C_6 alkyl, which may be branched or unbranched;

(iii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^{9}, SR^{9};

(iv) the group OR^{12}; and

(v) a halo group selected from F, Cl, Br and I.

18. The use according to Claim 17 wherein R^{5}, R^{6}, R^{7} and R^{8} are each independently selected from the group consisting of:

(i) hydrogen

(ii) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^{9}, SR^{6}, OCF_3 and CF_3; and

(iii) a halo group selected from F, Cl, Br or I.

19. The use according to Claim 18 wherein R^{5}, R^{6}, R^{7} and R^{8} are each independently selected from hydrogen, C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-3 alkoxy groups OR^{9}, wherein R^{9} is as defined as in Claim 1.

20. The use according to any preceding claim wherein R^2 and R^4 both represents methoxy.

21. The use according to any preceding claim wherein R^5 represents

(i) hydrogen

(ii) C_1 to C_6 alkyl which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9 or a halo group selected from F, Cl, Br and I;

(iii) C_6 to C_{10} aryl which may be unsubstituted or substituted with 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, F, Cl, Br, I, OCF_3 and CF_3; or

(iv) a halo group selected from F, Cl, Br and I.

22. The use according to any preceding claim wherein R^5 represents hydrogen, unsubstituted C_1 to C_6 alkyl, or a halo group selected from F, Cl, Br and I.

23. The use according to any preceding claim wherein R^5 represents hydrogen.

24. The use according to any preceding claim wherein R^6 represents

(i) hydrogen,

(ii) C_1 to C_6 alkyl which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of OR^9, SR^9 and a halo group selected from F, Cl, Br and I;

(iii) C_6 to C_{10} aryl which may be unsubstituted or substituted with 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, F, Cl Br, I, OCF_3 and CF_3; or

(iv) a halo group selected from F, Cl, Br and I.

25. The use according to any preceding claim wherein R^7 represents hydrogen, unsubstituted C_1 to C_6 alkyl, or a halo group selected from F, Cl Br and I.

26. The use according to any preceding claim wherein R^7 represents hydrogen.

27. The use according to Claim 1 wherein one of R^5, R^6, R^7 and R^8 is other than hydrogen, and the remaining three represent hydrogen.

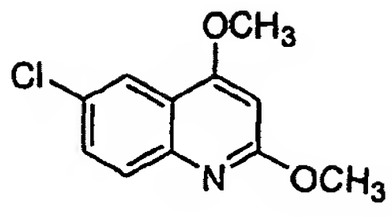
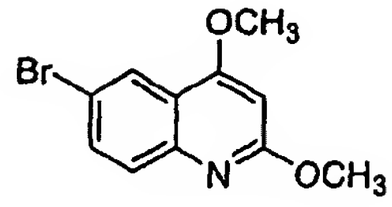
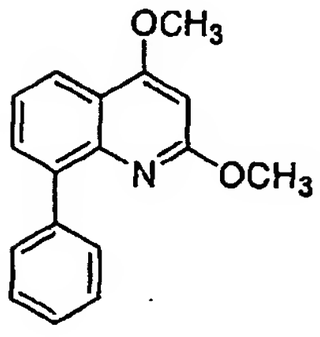
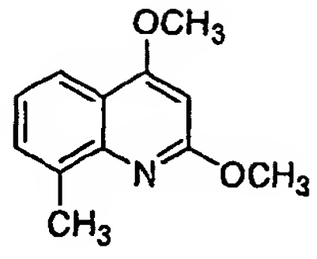
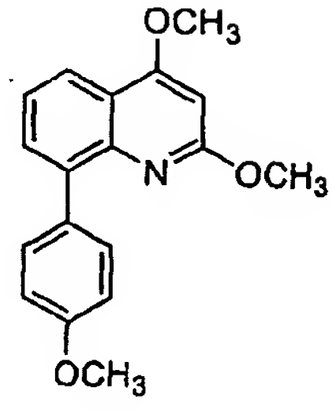
28. The use according to any preceding claim wherein R^9 represents unsubstituted C_1 to C_6 alkyl.

29. The use according to any preceding claim wherein R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of H and unsubstituted C_1 to C_6 alkyl.

30. The use according to any preceding claim wherein R^{12} represents unsubstituted C_1 to C_6 alkyl.

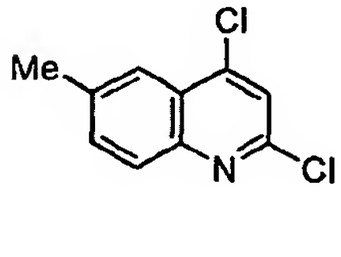
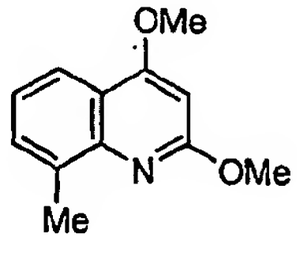
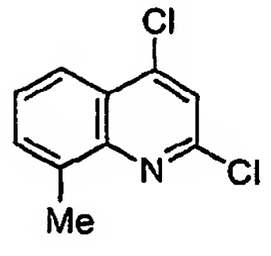
31. The use according to any preceding claim wherein R^1 represents H.

32. The use according to Claim 1 wherein the compound of Formula (I) has the structure:

and


33. The use according to Claim 1 wherein the compound of Formula (I) is selected from the group consisting of:



and


34. The use according to any preceding claim wherein the helminth is a nematode.

35. The use according to Claim 34 wherein the nematode is selected from the group consisting of: *Ostertagia lyrata, O. ostertagi, O. circumcincta, Cooperia oncophora, C. pectinata, C. punctata, C. surnabada, C. curticea, Haemonchus contortus, H. placei, Trichostrongylus axei, T. colubriformis, T. vetrinus, Bunostomum phlebotomum, B. trigonocephalum, Oesophagostomum radiatum, O. dentatum, O. venulosum, O. columbianum, Strongyloides papillosus, S. westeri, S. stercoralis, Nematodirus helvetianus, N. spathiger, N. filicolis, Trichuris spp., Strongylus vulgaris, S. edentatus, S. equinus, Triodontophorus spp.,*

Oxyuris equi, Parascaris equorum, Habronema muscae, Oncocerca spp., Dirofilaria immitis, Toxocara canis, Toxascaris leonina, Ancylostoma caninum, A. braziliense, A. duodenale, Thelazia spp., Uncinaria stenocephala, Chaberia ovina, Ascaris lumbricoides, Dictyocaulus vivaparus, D. arnfieldi, D. filaria, Brugia malayi, B. timori, Dioctophyma renale, Enterobius vermicularis, Loa loa, Mansonella ozzardi, M. perstans, M. streptocerca, Necator americanus, Onchocerca volvulus, Stronglyloides stercoralis, Trichinella spiralis, T. triciura and Wuchereria bancrofti.

36. The use according to Claim 35 wherein the nematode is a plant-damaging nematode selected from the genera *Meloidogyne, Heterodera, Ditylenchus, Aphelenchoides, Radopholus, Globodera, Pratylenchus, Longidorus* and *Xiphenema*.

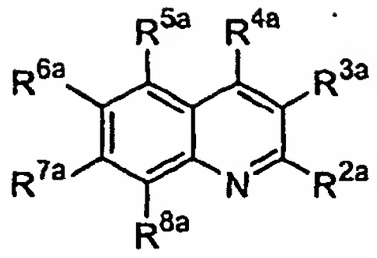
37. The use according to any of Claims 1 to 33 wherein the helminth is a cestode.

38. The use according to Claim 37 wherein the cestode is selected from the group consisting of *Diphyllobothrium latum, D. caninum, Echinococcus granulosus, E. multilocularis, Hymenolepsis diminuta, Taenia multiceps, T. saginatus, T. serialis, T. solium and Vampirolepis nana*.

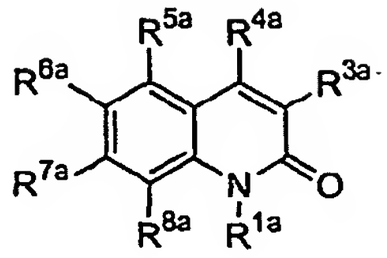
39. The use according to any of Claims 1 to 33 wherein the helminth is a trematode.

40. The use according to Claim 39 wherein the trematode is selected from the group consisting of *Clonorchis sinensis, Dicrocoelium dendriticum, an echinostome, Fasciolopsis buski, Fasciola hepatica, a heterophyid, Nanophyetus salmincola, Opisthorchis felineus, O. viverrini, Paragonimus kellicotti, P. westermani, Schistosoma haematobium, S. japonicum, S. mansoni, S. intercalatum* and *S. mekongi.*

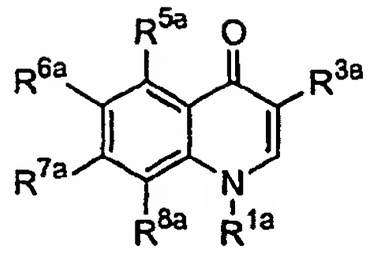
41. A compound of Formula (II), (IIA) or (IIB):



(II)



(IIA)



(IIB)

wherein:

R^{1a} represents H, C_1 to C_6 alkyl or benzyl

R^{2a} represents OR^{12} or SR^{12};

R^{4a} represents OR^{12} or SR^{12};

R^{3a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} is selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_{20} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_2 to C_{10} alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(v) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, $COOR^{10}$, COR^9, OCF_3, CF_3 and $NR^{10}R^{11}$;

(vi) C_3 to C_8 cycloalkyl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, OH, SH, NO_2, $COOR^{10}$, COR^9, OCF_3, CF_3 and $NR^{10}R^{11}$;

(vii) a heterocyclic group, which may be aromatic or non-aromatic, having from 5 to 10 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen or sulfur atoms and the remainder are carbon atoms;

(viii) OR^{12}; or

(ix) a halo group selected from F, Cl, Br or I;

with the proviso that at least one of R^{5a}, R^{6a}, R^{7a} and R^{8a} is selected from the group consisting of:

(i) C_2 to C_{10} alkenyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9 or SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(ii) C_2 to C_{10} alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_6 to C_{15} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) OR^{12}; or

(v) a halo group selected from F, Cl, Br or I,

wherein R^9 represents C_1 to C_6 alkyl or C_6 to C_{15} aryl;

R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of hydrogen, C_1 to C_6 alkyl and C_6 to C_{15} aryl; and

R^{12} represents C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

or an N-oxide derivative thereof, wherein the quinoline ring nitrogen forms an N-oxide group, or a pharmaceutically acceptable salt, or solvate, or addition salt or a quaternary ammonium salt thereof.

42. A compound according to Claim 41 wherein R^{3a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are independently selected from the group consisting of:

(i) hydrogen;

(ii) C_1 to C_6 alkyl, which may be branched or unbranched and unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iii) C_2 to C_6 alkynyl, which may be unsubstituted or substituted by 1-3 substituents independently selected from the group consisting of C_6 to C_{10} aryl, OR^9 or SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$ and $NR^{10}R^{11}$;

(iv) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(v) OR^{12} wherein R^{12}; and

(vi) a halo group selected from F, Cl, Br and I,

wherein R^9, R^{10}, R^{11} and R^{12} are as defined as in Claim 41.

43. A compound according to Claim 41 or Claim 42 wherein R^{3a} represents H.

44. A compound according to any of Claims 41 to 43 wherein R^{5a}, R^{6a}, R^{7a} and R^{8a} are selected from the group consisting of:

(i) hydrogen;

(ii) unsubstituted C_1 to C_6 alkyl which may be branched or unbranched;

(iii) unsubstituted C_1 to C_6 alkynyl, which may be branched or unbranched;

(iv) unsubstituted C_6 to C_{10} aryl;

(v) OR^{12}; or

(vi) a halo group selected from F, Cl, Br or I.

45. A compound according to any of Claims 41 to 44 wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} is other than hydrogen and the remaining three represent hydrogen.

46. A compound according to any of Claims 41 to 45 wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents a group selected from:

(i) C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, CN, F, Cl, Br, I, OH, SH, NO_2, COR^9, $COOR^{10}$, OCF_3, CF_3 and $NR^{10}R^{11}$;

(ii) OR^{12}; or

(iii) a halo group selected from F, Cl or Br,

and the remaining three represent hydrogen, wherein R^9, R^{10}, R^{11} and R^{12} are as defined in Claim 41.

47. A compound according to any of Claims 41 to 46 wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents C_6 to C_{10} aryl, which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, OR^9, SR^9, F, Cl, Br, I, OCF_3 and CF_3; and the remaining three represent hydrogen.

48. A compound according to any of Claims 41 to 47 wherein at least one of R^{6a} and R^{8a} represents a group selected from: F, Cl, Br, I and OR^{12} wherein R^{12} as defined as in Claim 41.

49. A compound according to any of Claims 41 to 48 wherein least one of R^{6a} and R^{8a} is selected from phenyl which may be unsubstituted or substituted by 1-5 substituents independently selected from the group consisting of C_1 to C_6 alkyl, C_6 to C_{10} aryl, F, Cl, Br, I, OCF_3, CF_3, OR^9 and SR^9 wherein R^9 represents C_1 to C_6 alkyl.

50. A compound according to any of Claim 49 wherein at least one of R^{6a} and R^{8a} is selected from phenyl which may be substituted by 1-3 methoxy groups.

51. A compound according to any of Claims 41 to 50 wherein R^{5a} represents hydrogen.

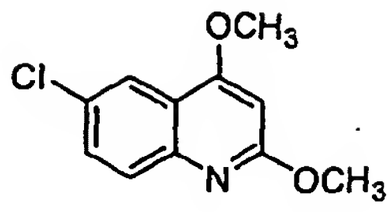
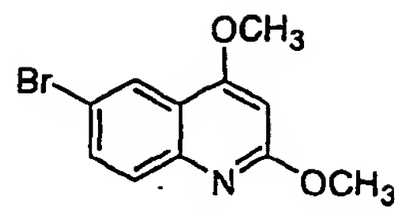
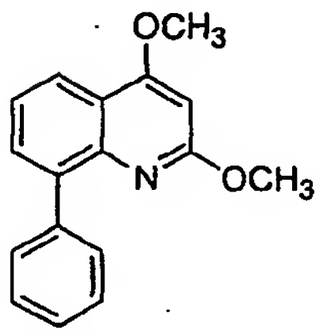
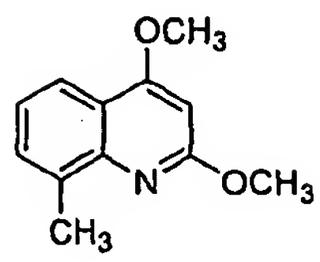
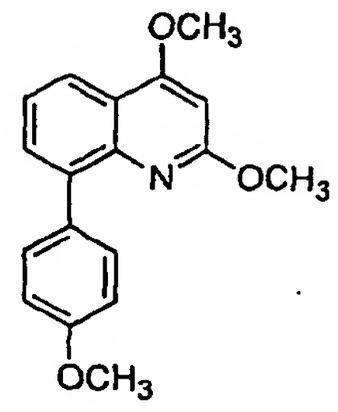
52. A compound according to any of Claims 41 to 51 wherein R^{7a} represents hydrogen.

53. A compound according to any of Claims 41 to 52 wherein R^9 represents unsubstituted C_1 to C_6 alkyl.

54. A compound according to any of Claims 41 to 53 wherein R^{10} and R^{11} are the same or different and each is independently selected from the group consisting of H and C_1 to C_6 alkyl.

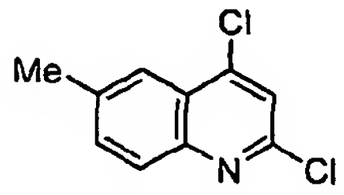
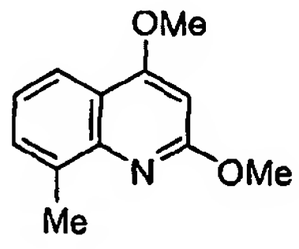
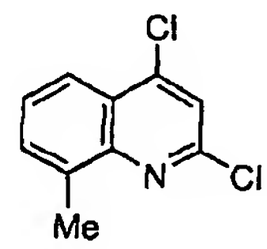
55. A compound according to any of Claims 41 to 54 wherein R^{1a} represents H.

56. A compound according to Claim 41 selected from the group consisting of:

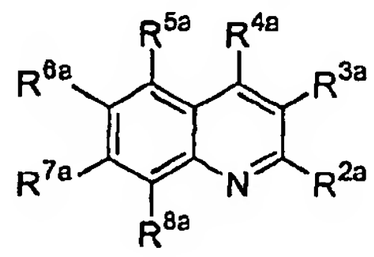
and


57. A compound according to Claim 41 selected from the group consisting of:



and


58. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to any of Claims 41 to 57 in a pharmaceutical carrier.

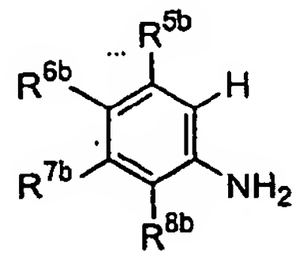
59. A process for the production of a compound of Formula (II):


(II)

or an intermediate thereof, wherein R^{2a} and R^{4a} represent OR^{12} or SR^{12} and R^{12} represents C_1 to C_6 alkyl, and R^{3a}, R^{5a}, R^{6a}, R^{7a} and R^{8a} are as defined in

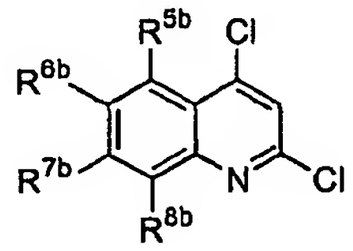
any of Claims 41 to 56, and are other than C_2 to C_{10} alkenyl, C_2 to C_{10} alkynyl, or C_6 to C_{15} aryl, comprising the steps of:

(a) subjecting a compound of Formula (III)



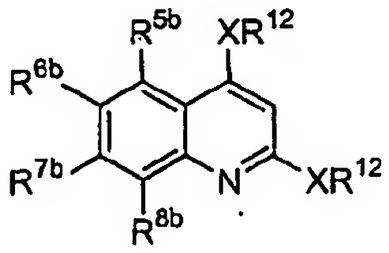
(III)

wherein R^{5b}, R^{6b}, R^{7b} and R^{8b} respectively represent the groups R^{5a}, R^{6a}, R^{7a} and R^{8a} or precursors thereof, to reaction with malonic acid in the presence of phosphorus oxychloride to produce a compound of Formula (IV):



(IV) ; and

(b) subjecting the compound of Formula (IV) to reaction with $NaXR^{12}$, wherein X represents oxygen or sulphur to form a compound of Formula (V):



(V)

and optionally,

(c) introducing a group R^{3a} or a precursor thereof, where R^{3a} is other than hydrogen, into the 3-position of the quinoline ring, by subjecting the compound of Formula (V) to a deprotonation reaction at the quinoline 3-position using a strong base, and quenching the

anion with an electrophile to form the group R^{3a} or a precursor thereof.

60. A process for producing a compound of Formula (II) or an intermediate thereof,. wherein at least one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents a substituent selected from substituted or unsubstituted C_2 to C_{10} alkenyl, substituted or unsubstituted C_2 to C_{10} alkynyl, substituted or unsubstituted C_6 to C_{15} aryl or a substituted or unsubstituted C_5 to C_{10} heteroaryl group as defined in any of Claims 41 to 56, comprising reacting a compound of Formula (II) wherein one of R^{5a}, R^{6a}, R^{7a} and R^{8a} represents Br, I or triflate, with a boronic acid derivative of Formula (VI):

$$(OH)_2B\text{-}\psi \qquad (VI)$$

wherein ψ represents a substituted or unsubstituted C_2 to C_{10} alkenyl, substituted or unsubstituted C_2 to C_{10} alkynyl, substituted or unsubstituted C_6 to C_{15} aryl or a C_5 to C_{10} heteroaryl group as defined as in any of Claims 40-55, the reaction being carried out in the presence of a base and a palladium or nickel catalyst under Suzuki coupling conditions.

61. A process according Claim 60 wherein the catalyst is selected from the group consisting of $Pd(PPh_3)_4$, $Ni(dppf)Cl_2$ $Pd(dba)_2$, $Pd(OAc)_2$, $Pd(OAc)_2/(o\text{-}tol)_3P$, $Pd(OAc)_2/dppf$, $(PhCN_2PdCl_2/Ph_3As$, $(CH_3CN)_2PdCl_2$, Pd-C, $(Ph_3P)_2NiCl_2$, $Pd(dppb)Cl_2$, bis(tricyclohexyl-phosphine)palladium(II) chloride, $(Ph_3P)_2PdCl_2$ and trans-di-μ-acetatobis[2-(di-o-tolylphosphino)-benzyl]dipalladium(II).

62. A process according to Claim 61 wherein the catalyst is selected from $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$.

63. A process according to any of Claims 60 to 62 wherein the base is selected from Na_2CO_3, $NaHCO_3$, K_2CO_3, Cs_2CO_3, K_3PO_4, Et_3N, Ag_2O, $Ba(OH)_2$ and CsF.

64. A process according to Claim 63 wherein the base is Na_2CO_3.

65. A process according to any of Claims 60 to 64 wherein the reaction is carried out in a solvent comprising a hydrocarbon.

66. A process according to Claim 65 wherein the solvent comprises a hydrocarbon selected from toluene and benzene.

67. Use according to Claim 1, of a compound of Formula (I), (IA) or (IB) as defined in any of Claims 1 to 33, in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of infections caused by arthropod ectoparasites.

68. Use according to Claim 67 wherein the arthropod ectoparasites are selected from the group consisting of flies, lice, keds, fleas, ticks, mites and certain copepod of fish.

69. Use according to Claim 68 wherein the arthropod ectoparasites are ticks selected from the group consisting of *Boophilus* spp, *Rhipicephalus* spp, *Ixodes* spp, *Hyalomma* spp, *Amblyomma* spp, *Dermacentor* spp and *Argas* spp.

70. Use according to Claim 68 wherein the arthropod ectoparasites are mites selected from the group consisting of *Psoroptes* spp, *Chorioptes* spp, *Sarcoptes* spp and *Demodex* spp.

71. Use according to Claim 68 wherein the arthropod ectoparasites are flies selected from the group consisting of *Musca* spp, *Stomoxys* spp, *Oestrus*

spp, *Culicoides* spp, *Tabanus* spp, *Phlebotomus* spp, *Simulium* spp, *Lucilia* spp, *Calliphora* spp, *Dermatobia* spp and *Hypoderma* spp.

72. Use according to Claim 68 wherein the arthropod ectoparasites are lice selected from the group consisting of *Linognathus* spp, *Bovicola* spp, *Haematopinus* spp and *Solenopotes* spp.

73. Use according to Claim 68 wherein the arthropod ectoparasites are keds.

74. Use according to Claim 73 wherein the ked is *Melophagus ovinus*.

75. Use according to Claim 68 wherein the arthropod ectoparasites are fleas.

76. Use according to Claim 75 wherein the flea is *Ctenocephalides* spp.

77. Use according to Claim 68 wherein the arthropod ectoparasite is an ectoparasite of fish.

78. Use according to Claim 77 wherein the ectoparasite is a copepod parasite selected from the group consisting of *Lepeophtheirus salmonis* and *Caligus elongatus*.

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB 01/04337

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/18 C07D215/22 C07D215/26 C07D215/20 C07D215/40
A61K31/47 A61K31/4704 A61P33/10 A61P33/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WARNER P ET AL: "QUINOLINE ANTIFOLATE THYMIDYLATE SYNTHASE INHIBITORS: VARIATION OF THE C2- AND C4-SUBSTITUENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 15, 24 July 1992 (1992-07-24), pages 2761-2768, XP001036970 ISSN: 0022-2623 see compound 10v page 2763 --- -/--	57

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2002	07/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schmid, J-C

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB 01/04337

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SHAH V.R. ET AL.: "A new synthesis of 2,4-dihydroxyquinolines" J. SCI. INDUSTR. RES., vol. 19B, 1 May 1960 (1960-05-01), page 176 XP002188550 left-hand column, line 24 - line 26 table 1 ---	57
A	PERRETT S ET AL: "ATANINE (3-DIMETHYLALLYL-4-METHOXY-2-QUINOLONE), AN ALKALOID WITH ANTHELMINTIC ACTIVITY FROM THE CHINESE MEDICINAL PLANT, EVODIA RUTAECARPA" PLANTA MEDICA, THIEME, STUTTGART, DE, vol. 61, 1995, pages 276-278, XP001036998 ISSN: 0032-0943 cited in the application the whole document ---	32,33, 56,57
A	DE 36 37 649 A (FED. REP. GER.) 14 April 1988 (1988-04-14) column 2, line 51 -column 3, line 14 see Norfloxazin column 3, line 46 - line 50 ---	32,33, 56,57
A	LEE, BYUNG H. ET AL: "Anthelmintic.beta.-hydroxyketoamides (BKAS)" BIOORG. MED. CHEM. LETT. (1998), 8(23), 3317-3320 , XP004143750 see compound 9 page 3318 ---	32,33, 56,57
A	IBARRA, O. F. ET AL: "The relevance of in vitro anthelmintic screening tests employing the free-living stages of trichostrongylid nematodes" J. HELMINTHOL. (1984), 58(2),. 107-12 , XP001036823 table III ---	32,33, 56,57

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INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/GB 01/04337

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 92, no. 17, 28 April 1980 (1980-04-28) Columbus, Ohio, US; abstract no. 141168, KOVALENKO, F. P.: "Selection in vitro of antialveococcal and antiechinococcal preparations" XP002188553 see 8-Quinolinol, 5,7-diiodo-(RN-83-73-8) and Quinoline,4-(4-methyl-1-piperazinyl)-(RN-54797-33-0) abstract & DEPOSITED DOC. (1978), VINITI 3276-78, 15 PP. AVAIL.: VINITI, ---	32,33, 56,57
A	US 5 227 387 A (DREIKORN BARRY A ET AL) 13 July 1993 (1993-07-13) cited in the application the whole document ---	32,33, 56,57
A	KALLURAYA, BALAKRISHNA ET AL: "Synthesis and pharmacological properties of some quinoline derivatives" FARMACO (1998), 53(6), 399-404 , XP002188551 the whole document ---	32,33, 56,57
A	TEWARI, SWATI ET AL: "Syntheses and antifilarial profile of 7-chloro-4-(substituted amino) quinolines: a new class of antifilarial agents" BIOORG. MED. CHEM. LETT. (2000), 10(13), 1409-1412 , XP004222118 table 2 ---	32,33, 56,57
A	WO 95 07894 A (HOECHST SCHERING AGREVO GMBH) 23 March 1995 (1995-03-23) see compound 399 claim 1 ---	32,33, 56,57
A	GO, MEILIN ET AL: "Synthesis of some novel amodiaquine analogs as potential antimalarial and antifilarial compounds" J. MED. CHEM. (1981), 24(12), 1471-5 , XP002188552 the whole document ---	32,33, 56,57

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INTERNATIONAL SEARCH REPORT

Int ial Application No
PCT/GB 01/04337

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category •	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SINGH, JUJHAR ET AL: "Chemotherapy of filariasis-on the search of new agents effective on the reproductive system of female adult worms" Z. NATURFORSCH., C: BIOSCI. (1990), 45(11-12), 1210-14 , XP001027282 page 1212; table II	32,33, 56,57
A	FR 2 205 327 A (SANDOZ SA) 31 May 1974 (1974-05-31) claim 1; example 4	56,57
A	YOSHINOBU T. ET AL: JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 34, no. 6, November 1997 (1997-11), pages 1677-1683, XP001027322 ISSN: 0022-152X the whole document	56,57

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-31, 34-55, 58-78

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of the compounds for the claimed use. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely claims 32,33,56 and 57.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Application No
PCT/GB 01/04337

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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